

RECENT ADVANCES IN  
ORGANIC CHEMISTRY



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RECENT ADVANCES IN  
PHYSICAL AND INORGANIC  
CHEMISTRY

By A. W. Stewart, D.Sc.  
and C. L. Wilson, M.Sc., Ph.D.



# RECENT ADVANCES IN ORGANIC CHEMISTRY

*by*

ALFRED W. STEWART, D.Sc.

AND

HUGH GRAHAM, D.Sc.

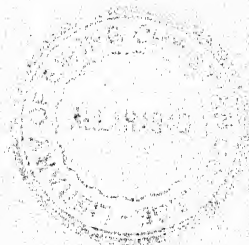
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VOLUME II

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#### PUBLISHER'S NOTE

Volume I, which can no longer be regarded as dealing with recent advances in organic chemistry and is therefore mainly of historical interest, is now out of print.

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## PREFACE

THIS edition — the seventh — of *Recent Advances in Organic Chemistry*, on account of the many interesting and important developments in Organic Chemistry, has been re-arranged as Volumes II and III of the series.

In each volume the sections have been revised and extended to include new work, and in the cases of the polysaccharides, diterpene and triterpene compounds, where advances have been very rapid, a separate chapter has been given to each of these three groups. New chapters on Pectic Substances and Alginic Acid, Lignans, Porphyrins, Azaporphyrins, Synthetic High Polymers and Condensates, Deutero-Organic Compounds, and Some Aspects of Stereochemistry have been added. Inspection of the tables of contents will show how these topics have been arranged in the two volumes.

The references to the literature are indicated by figures, whilst footnotes are distinguished by asterisks. In the index of each volume the principal reference is in heavier type.

The two books will, it is hoped, serve to guide the reader in the fields with which they deal, and encourage him to go further in the study of the various subjects discussed, since this is the main function of a work of this kind.

In preparing these volumes I was fortunate in having the advice and counsel of Professor A. W. Stewart before his untimely death in June 1947.

In conclusion I desire to acknowledge the great assistance which has been given to me by Dr. R. C. Pink, who undertook the onerous task of proof-reading, and I am further indebted to him for many helpful suggestions, which have led to improvements in the text.

HUGH GRAHAM.

The Queen's University of Belfast,  
March 1948.

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# RECENT ADVANCES IN ORGANIC CHEMISTRY

## CHAPTER I

### ORGANIC CHEMISTRY IN THE TWENTIETH CENTURY

IN the form in which it exists to-day, organic chemistry may be said to take its root in the work of Frankland<sup>1</sup> at the middle of last century. Once the doctrine of the constancy of valency was accepted, the way was open for Couper<sup>2</sup> and Kekulé<sup>3</sup> to bring order into the vast mass of material which had been accumulated in earlier times; while, later, van't Hoff<sup>4</sup> and Le Bel<sup>5</sup> carried the ideas of molecular arrangement out of two dimensions into three and laid the foundation of our present views. Following in the track of these pioneers, the chemists of the latter half of the nineteenth century rapidly developed the theoretical side of the subject; while, on the other hand, the modern formulæ lent to synthetical work a certainty which had previously been unknown.

Despite the Briarean efforts of the synthetic school, it is safe to say that the latter half of the nineteenth century will be regarded as a time when theoretical speculation played the main part in the development of the subject. Of the hundred thousand organic compounds prepared during that time, the majority were still-born and their epitaphs are inscribed in Beilstein's Handbook. Compared with the great clarifying process which laid the basis of our modern views, they weigh but little in the balance.

<sup>1</sup> Frankland, *Phil. Trans.*, 1852, 142, 417.

<sup>2</sup> Couper, *Phil. Mag.*, 1858, iv., 16, 104.

<sup>3</sup> Kekulé, *Annalen*, 1866, 137, 129.

<sup>4</sup> van't Hoff, *Voorstell tot uitbreiding der structuur formules in de ruimte* (1874).

<sup>5</sup> Le Bel, *Bull. Soc. chim.*, 1874, ii., 22, 377.

The new century opened under different auspices. At first it seemed as though the discoveries in electronic physics would have their reaction upon our structural views; but though several attempts<sup>1</sup> had been made in this region of the subject, organic chemists in general did not welcome them with anything like whole-hearted encouragement. There was a feeling, apparently, that in abandoning the usual structural formulæ and replacing them by electronic symbols the subject was being complicated instead of simplified.

During the last fifty years the flood of synthetic material, principally from the German laboratories, has tended to obscure the genesis of what we still, out of respect for tradition, term organic chemistry. In its early days the science was devoted to the study of compounds produced by natural methods in plants and animals; and it is interesting to find that during the new century a return has been made to the older field.

The twentieth century was hardly begun, when in 1903 Komppa devised a synthesis of camphor, and thus cleared up a problem which had engaged the attention of many investigators. Later came the work of Perkin and his school in the terpene group, which gave a fresh impetus to study in this branch of the subject.

In the alkaloid series great strides have been made, both in determining constitutions and in devising synthetic methods of preparing the natural substances; whilst the examination of plants and the extraction from them of new alkaloids is proceeding apace.

In the carbohydrate group the problem which looms behind most of the modern investigations is the constitution of the celluloses. The celluloses have extremely complicated structures; and it was only by breaking up their molecules into simpler compounds and then identifying these that we could hope to determine the constitution of the parent substance.

<sup>1</sup> Nelson and Falk, *School of Mines Quarterly*, 1909, 30, 179; *J. Amer. Chem. Soc.*, 1915, 37, 274; Nelson, Beans, and Falk, *ibid.*, 1913, 35, 1810; Falk and Nelson, *ibid.*, 1910, 32, 1637; 1911, 33, 1140; Falk, *ibid.*, 1912, 34, 1041; Noyes, *ibid.*, 1912, 34, 663; Fry, *ibid.*, 1912, 34, 664; 1914, 36, 248, 262, 1035; 1915, 37, 885; 1916, 38, 1323, 1327, 1333; *Zeitsch. physikal. Chem.*, 1911, 76, 385, 398, 591; 1912, 80, 29; 1913, 82, 665; 1915, 90, 458; Stark, *Jahrb. Radioaktiv. Elektronik*, 1908, 5, 124; 1909, 6, 12; 1912, 9, 15; *Physikal. Zeitsch.*, 1912, 13, 585; G. N. Lewis, *Valence* (1923).

The first step in this direction was evidently to obtain and identify readily purifiable carbohydrate derivatives such as methyl ethers, acetyl derivatives, etc. Then by methylating or acetylating celluloses themselves previous to breaking them up, it is possible to recognize among the decomposition products certain well-defined fragments which permit of guesses being made at the structure of the original molecule. This method in the hands of Purdie, Irvine and their collaborators \* gave us the key to the constitution of cotton cellulose; and with the road open, it was not unreasonable to expect a rapid increase in our knowledge of this field.

Much more complicated is the riddle of the protein molecules. Although there is a surface similarity between proteins and celluloses owing to the fact that both molecular types are liable to fission under the action of hydrolysing agents, the decomposition products of the proteins are far more complex than those resulting from the break-down of celluloses. Fischer's work on the polypeptides has been a first step towards a more exact knowledge of the protein constitutions; but it is a very short step on a very long road.

The methods devised by Fischer in his investigation of the polypeptides served him later in his researches on the tannins.† In 1912, he put forward the view that the natural tannins were fully esterified glucoses in which digalloyl nuclei replaced the hydrogen atoms of hydroxyl groups; and this conception of the tannin structure was justified by his synthesis of penta-(*m*-digalloyl)- $\beta$ -glucose, which closely resembles Chinese tannin in its properties. It must not be too hastily assumed, however, that Fischer's researches have furnished a key to the structure of all classes of tannins.

Turning to natural pigments, it will be found that the present century has seen a great advance in our knowledge. Kostanecki's researches on the flavone derivatives established the constitutions of many of the natural dyes. Willstätter's and Fischer's work on chlorophyll ‡ has given us insight into the nature of that substance, whilst in the field of flower pigments Willstätter has established the general character of the anthocyanins § and has practically reduced future work to a stereotyped line.

\* See Chapter II.

† See Chapter V., Vol. III.

‡ See Chapter XI

§ See Chapter X.

The examination of the colouring matters of the blood\* and of the bile\* has opened up yet another branch of pure "organic chemistry"; and the parallelism established between hæmin and chlorophyll suggests most interesting reflections as to the origin of these two natural substances which play so great a part in animal and vegetable economy.

So much for the effects of a return to the original aims of organic chemistry. When the purely synthetic side of the subject is examined, it must be admitted that, with some notable exceptions, the results are of much less general interest. Of new compounds there is no lack, certainly; but there is a distinct dearth of interesting materials. One or two examples may be given here of substances which have an interest for chemists other than the mere specialist.

The discovery of the ketens by Staudinger brought to light a completely fresh class of substances of remarkable reactivity; and the problem of the relative activities of the carbonyl and ethylenic bonds in these compounds promises eventually to throw light upon some aspects of chemical linkages. Work in the field of the ketens has also clarified our ideas with regard to the nature of the aliphatic diazene derivatives.

By far the most interesting set of compounds prepared in the last quarter of a century has been the derivatives of various elements in a state of abnormal valency. Gornberg's triphenyl-methyl seemed at first likely to remain without a parallel; but in recent times a perfect flood of abnormalities has been let loose by further investigation. The aryl derivatives of the alkali metals, the metal-ketyls,† the tri-aryl-methyl series, to name only a few, have forced upon the notice of chemists the fact that the old and apparently well-tried dogma of the permanent quadrivalence of carbon is in a very shaky condition. By the researches in these and allied fields,‡ carbon has been definitely ranked among the ionogenic elements; and the way was made open for the ready acceptance of G. N. Lewis's general theory of valency on the electronic basis.

On the technical side organic chemists have not been idle. The great dye industry pours out its flood of colour; and although

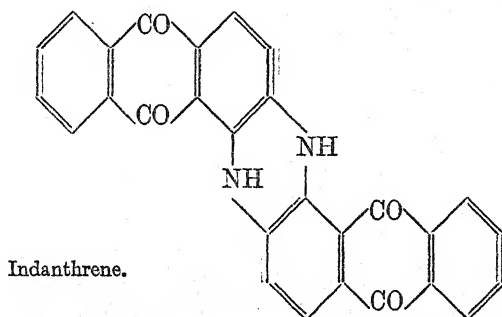
\* See Chapter V., Vol. III.

† See Chapter XIII., Vol. III.

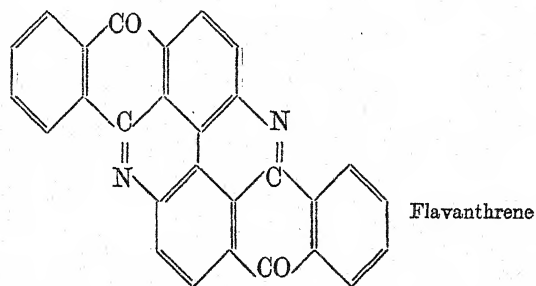
‡ See Chapter XIV., Vol. III.

as a general rule its products have a commercial rather than a scientific interest, two classes deserve notice here.

Vat dyes are those which, like indigo, are almost insoluble in water, but yield on reduction leuco-compounds soluble in alkali. The actual dyeing process is carried out by impregnating the fabric with the leuco-compound and then allowing or forcing oxidation to take place. The earliest example of the anthraquinone vat dyes, indanthrene, was produced in 1901. It is prepared by fusing 2-amino-anthraquinone with alkali, or by condensing 1-amino-anthraquinone with itself:—



To the same class belongs flavanthrene:—

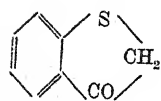
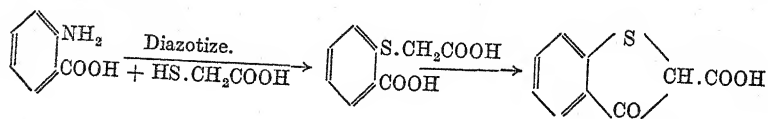


which can be produced by heating 2-amino-anthraquinone with alkali to a temperature higher than that required to form indanthrene. Indanthrene is a valuable dye-stuff of greater stability than indigo; whilst flavanthrene, though giving a blue vat, dyes cotton yellow.

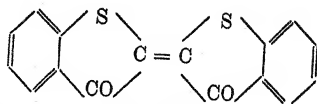
Another class of anthraquinone vat dyes are the acyl derivatives of amino-anthraquinones. For the most part these are

yellow or orange in colour, whilst the anthraquinone-imines vary in tint from orange to red or claret colour according to their constitution.

In 1906 Friedländer<sup>1</sup> discovered the thio-analogue of indigo in which the two imino groups are replaced by sulphur atoms; and this substance has become the foundation of a very extensive group of dyes. The following scheme shows one method of synthesis:—

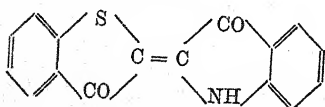


Thio-indoxyl.

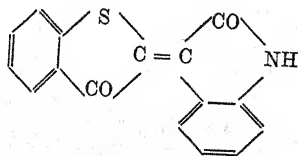


Thio-indigo.

Thio-indigo imparts a reddish-violet colour to the fabric, and modified tints can be produced by using the amino or halogen derivatives. Further changes in colour are obtained by condensing together one isatin and one thio-indoxyl group, producing mixed structures:—

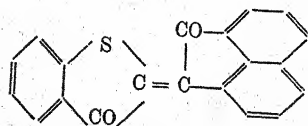


Violet A.



Scarlet.

whilst by uniting thio-indoxyl with diketo-acenaphthenequinone the valuable dye thio-indigo scarlet is obtained:—

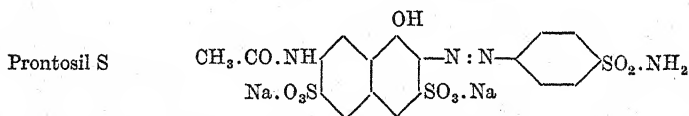
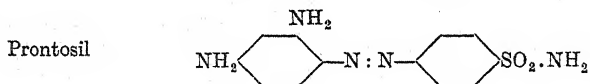
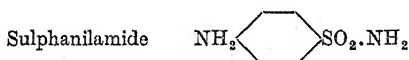


<sup>1</sup> Friedländer, *Ber.*, 1906, 39, 1060.

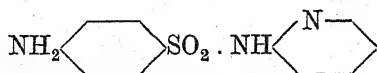


Synthetic drugs have been produced in large numbers in recent years. Of these one of the most important is salvarsan or 606 which is dihydroxy-diamino-arsenobenzene-dihydrochloride. It has been used with success to kill the spirochæte which produces syphilis, though, of course, it has no effect in repairing the ravages already caused by the disease if treatment has been delayed. Modifications of salvarsan now largely in use are neoarsphenamine and sulpharsphenamine, the formaldehyde-sulphoxylate and formaldehyde-bisulphite derivatives respectively. Another organic arsenic derivative employed is atoxyl (also known as arsamin or soamin) which is the mono-sodium salt of *p*-aminophenyl-arsenic acid. It is chiefly utilized in cases of sleeping sickness. Both drugs, if used incautiously, may produce blindness.

The application of sulphanilamide, prontosil, and their congeners in chemotherapy is claimed, not unjustly, as marking one of the most important advances in chemical warfare against disease. The formulæ of three principal members of the group are these :

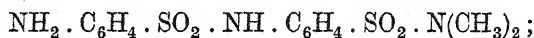


By using sulphanilamide, many successful results have been observed in cases of diseases produced by gonococci, meningococci, pneumococci, and staphylococci. Improvement has also been noted in patients suffering from gas gangrene, typhoid fever, undulant fever, and some affections of the skin. It is, however, too early yet to expect unanimous agreement about these drugs, for unfortunately their use is not altogether devoid of risk, since in certain cases toxic effects have been observed. The pyridine derivative known as M. & B. 693 or T. 693 has the following structure :—

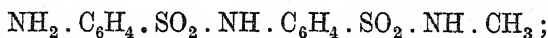


This has yielded valuable results in cases of broncho- and lobar-pneumonia, pneumococcal meningitis and gonorrhœa. Curiously enough, prontosil showed a high bactericidal action *in vivo* whereas experiments *in vitro* yielded poor results. The reason for this is found in the discovery<sup>1</sup> that in the animal body prontosil is decomposed and sulphanilamide is produced, which suggests that the latter is the real active agent. In certain cases, the so-called Disseptals, A, B, and C, have been found to be better than some of the prontosil derivatives. The formulæ for these compounds are:

Disseptal A—



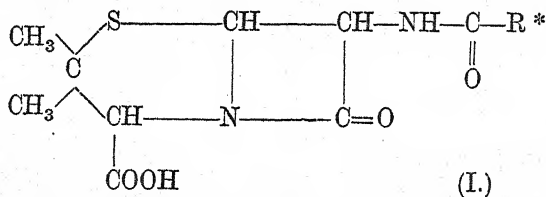
Disseptal B—



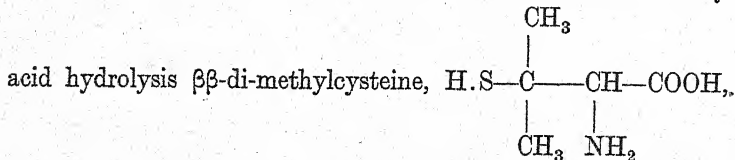
and Disseptal C, the parent substance—



The curtain of secrecy which surrounds chemical work on penicillin has been partially raised. Several penicillins have been isolated, and the general structure (I.) is considered to explain satisfactorily the known facts.



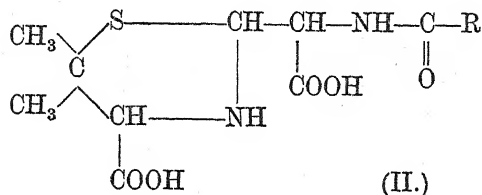
The study of the products of acid and alkaline hydrolysis of the penicillins has yielded important constitutional information. By



<sup>1</sup> Fuller, *Lancet*, 1937, 232, 194.

\* R represents the  $\Delta^2$ -pentenyl (in penicillin I. or F), benzyl (in penicillin II or G), *p*-hydroxybenzyl (in penicillin III. or X) or *n*-heptyl (in penicillin K) group.

and hexenoylaminoacetaldehyde,  $\text{C}_5\text{H}_9\text{—CO—NH—CH}_2\text{—CHO}$ , have been obtained from penicillin I., and phenylacetylaminacetaldehyde,  $\text{C}_6\text{H}_5\text{—CH}_2\text{—CO—NH—CH}_2\text{—CHO}$ , from penicillin II. Alkaline hydrolysis gave rise to penicilloic acids, which have been shown by synthesis to be thiazolidines of the general structure (II.)

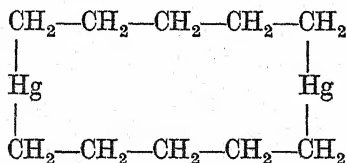


Other reactions and X-ray examination support this structural arrangement for the penicillins.

Numerous new local anæsthetics are now known, such as stovaine, novocaine, and  $\beta$ -eucaine, and the simpler compounds ethylene and ethyl chloride are used as general anæsthetics. A mixture of ethylene and oxygen containing 80 to 90 per cent. of the former has proved a valuable anæsthetic for most major operations. Adrenaline has been synthesized; and the constituents of ergot are now manufactured for pharmaceutical purposes.

In the field of simple mono-heterocyclic compounds, a considerable extension of our knowledge has been made; and at the present time the catalogue of elements which can play their part as members of ring-compounds is large compared with the list of three—oxygen, sulphur, and nitrogen—which originally represented the limit of our knowledge in this branch.

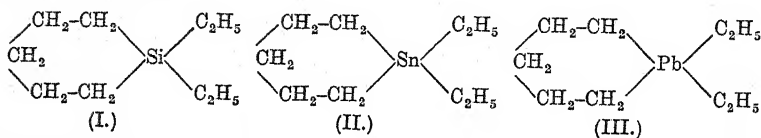
Mercury yields a remarkable twelve-membered ring <sup>1</sup>



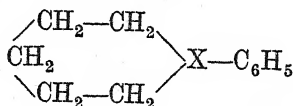
by the action of 1, 5-dibromopentane on sodium amalgam. Curiously enough, the six-membered compound containing one mercury atom in the ring was not obtained in this reaction. By

<sup>1</sup> Hilpert and Grüttner, *Ber.*, 1914, 47, 186.

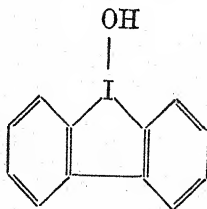
action on silicon chloride with a Grignard reagent prepared from 1, 5-dibromopentane and subjecting the dichloro-derivative thus formed to the action of methyl-magnesium bromide, it is possible to obtain the six-membered ring (I.). The analogous tin and lead compounds (II.) and (III.) are obtained by the direct action of the Grignard reagent on diethyl-tin dichloride<sup>1</sup> and diethyl-lead dibromide.<sup>2</sup>



In parallel with nitrogen, the elements phosphorus,<sup>3</sup> arsenic,<sup>4</sup> antimony<sup>5</sup> and bismuth<sup>6</sup> have now been found capable of yielding ring-compounds of the type :



wherein X represents the atom of the trivalent element. In each case the mode of preparation is by the action of the phenyl-dichloro-derivative of the element upon a Grignard reagent prepared from 1, 5-dibromopentane. The selenium analogue of thiophen has been obtained<sup>7</sup>; and tellurium is now known as a ring-member.<sup>8</sup> Finally iodine has been found acting as a ring-member in diphenyl-iodonium hydroxide<sup>9</sup>; and Collie and



<sup>1</sup> Grüttner, Krause and Wiernik, *Ber.*, 1917, 50, 1549.

<sup>2</sup> Grüttner and Krause, *Ber.*, 1916, 49, 2666.

<sup>3</sup> Grüttner and Wiernik, *Ber.*, 1915, 48, 1473.

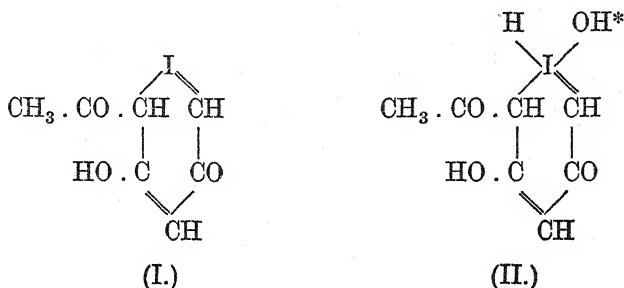
<sup>4</sup> *Ibid.*, 1915, 48, 1479. <sup>5</sup> *Ibid.*, 1915, 48, 1484. <sup>6</sup> *Ibid.*, 1915, 48, 1475.

<sup>7</sup> Foa, *Gazzetta*, 1909, 39, II., 527; compare Briscoe and Peel, *J.*, 1928, 1741.

<sup>8</sup> Morgan and Drew, *J.*, 1920, 117, 1456; 1924, 125, 731, 1601; Morgan and Burgess, *J.*, 1928, 321; Drew, *J.*, 1926, 223; Drew and Thomason, *J.*, 1927, 116.

<sup>9</sup> Mascarelli and others, *Gazzetta*, 1908, 38, II., 619; 1911, 41, I., 63, 68; 1912, 42, I., 101; 1913, 43, I., 26.

Reilly<sup>1</sup> by the action of iodine on the barium salt of diacetyl-acetone, have obtained a compound which appears to have the following structure (I.) :



It is interesting to note that this last substance in aqueous solution is strongly acidic, which differentiates it sharply from all previous alkyl derivatives of iodine. This is probably due to the formation of the hydrated form (II.) in which there is a double bond in the 3 : 4-position to the acidic hydrogen marked with the asterisk, as is required by the Vorländer Rule.

On the theoretical side of organic chemistry, to which we must now turn, Thiele's views on valency exerted a considerable influence during the century. It is very seldom that any theory is accepted immediately after being published ; usually a considerable time is required during which the chemical world assimilates the author's views in a more or less unconscious manner, until some day they find their way into text-books. It is a remarkable tribute to the value of Thiele's partial valency theory that it became a classic almost as soon as it was published.

From the Thiele theory we may pass to the problem of benzene, since the two questions hinge upon one another at some points. During the last twenty years, the constitution of benzene has been discussed from almost every possible standpoint, and we are certainly not less wise than when the discussion began. Whether we are wiser is a more doubtful matter. Certainly much can be learned from the arguments adduced by the various writers who have dealt with the subject ; and a perusal of the polemic is by no means a waste of time. The benzene problem in its present condition might well be described

<sup>1</sup> Collie and Reilly, *J.*, 1921, 119, 1550.

in the words used by some one to define Philosophy: "It is a subject in which the conclusion reached is of less importance than the means by which that conclusion is attained."

Linked with the problem of the constitution of benzene is another, which deals with the orientation of substituents in the benzene ring and the apparent directing influence which certain substituents exert upon the position taken up by a fresh incoming substituent.<sup>1</sup> This problem in turn has been brought into relationship with hypotheses with regard to the polarity of atoms in chains.

Passing to other subjects, intramolecular change must be mentioned, as in this region much work of first-class importance has been carried out since the beginning of the century. It would lead us too far were we to enter into any general discussion of the problem; but one or two examples must be given.

The most striking of these is the discovery by Hantzsch of a new class of electrolytes which have been named pseudo-acids and pseudo-bases.\* Previous to his work, the electrolytes known to us might be grouped under the four following heads: (1) Acids, which give rise to hydrogen ions; (2) Bases, which yield hydroxyl ions; (3) Salts, which dissociate into acidic and basic ions; and (4) Amphoteric electrolytes, which are capable of producing either hydrogen or hydroxyl ions according to the experimental conditions employed.

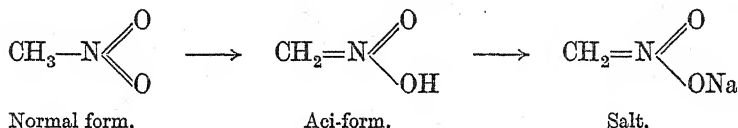
Now when an acid solution is neutralized by means of a base, the solution is acidic at the beginning and remains acidic all through the titration until the neutralization-point is reached. On the other hand, if we start with a solution of nitromethane, it is neutral in reaction; and yet if we slowly add to it a solution of sodium hydroxide, the solution does not become alkaline at once. In fact, we may have to add a considerable quantity of alkali before the next drop produces an alkaline reaction in the liquid. Clearly nitromethane is a neutral substance which, *given time*, can exhibit acidic properties in presence of alkali. It is this *slow neutralization* which distinguishes it from a true acid.

<sup>1</sup> For information on the subject, see Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (1910), and Obermiller, *Die orientierenden Einflüsse und der Benzolkern* (1909).

\* An account of this field is to be found in Stewart's *Physico-chemical Themes*.



Without going into the details of the evidence, it may be said that intramolecular change is the governing factor in the problem. True nitromethane is not acidic; but in presence of bases it may change into an isomeric body, the *aci-form*, which possesses a hydrogen capable of being replaced by alkali: so that the reaction may be represented by the following scheme:—



The slowness with which nitromethane neutralizes alkalis is obviously due to the fact that the intramolecular change from the normal to the aci-form is not instantaneous, but requires time for its accomplishment.

- The discovery of the pseudo-acids resulted in the collapse of Ostwald's hypothesis as to the nature of indicators. Ostwald<sup>1</sup> assumed that indicators underwent a change of colour when dissociated into their ions. Thus undissociated phenolphthalein, in his view, was colourless; but when converted into the easily dissociable sodium salt it broke down into ions which were red in colour. By adding acid to the alkaline solution, the dissociation of the phenolphthalein was restricted; and hence the colour disappeared. Stieglitz<sup>2</sup> suggested, on the other hand, that the production of the colour was due to intramolecular change in the phenolphthalein molecule; and Hantzsch<sup>3</sup> confirmed this, showing that phenolphthalein, for example, changes from the benzenoid to the quinonoid structure under the influence of alkali.

In connection with intramolecular change the case of tetranitromethane may be mentioned.<sup>4</sup> Under normal circumstances, this substance appears to exist in the pure "nitro" form (I.), but in presence of amines or alkyl sulphides it seems slowly to be converted into trinitro-nitrito-methane (II.), as it gives exactly

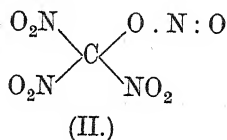
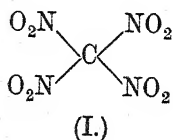
<sup>1</sup> Ostwald, *Die wissenschaftlichen Grundlagen der analytischen Chemie* (1894).

<sup>2</sup> Stieglitz, *J. Amer. Chem. Soc.*, 1903, 25, 112.

<sup>3</sup> Hantzsch, *Ber.*, 1906, 39, 1090.

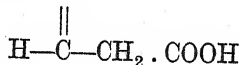
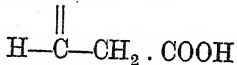
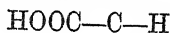
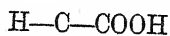
<sup>4</sup> Harper and Macbeth, *T.*, 1915, 107, 87; Macbeth, *ibid.*, 1824.

the same colour reactions as are observed in the case of alkyl nitrites:—

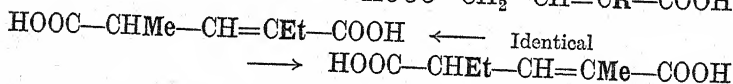
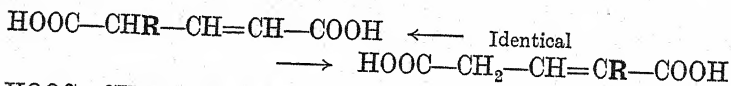


This case seems to be a half-way stage towards pseudo-acid formation.

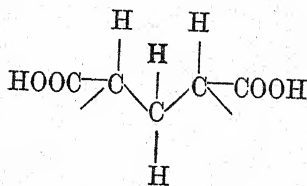
Some of the most surprising results obtained in recent years in the field of isomeric change are those due to Thorpe and his collaborators.<sup>1</sup> Glutaconic acid is known in only one form, though theoretically it should exist in the two stereoisomeric modifications whose formulæ are shown below:



Still more strange is the fact that when an  $\alpha$ -alkylglutaconic acid is prepared, it is found to be identical with  $\gamma$ -alkylglutaconic acid; and  $\alpha$ -methyl- $\gamma$ -ethylglutaconic acid is identical with  $\gamma$ -methyl- $\alpha$ -ethylglutaconic acid.

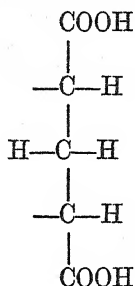


In order to account for these facts, it is assumed that the constitution of glutaconic acid is best represented by some formula such as this:



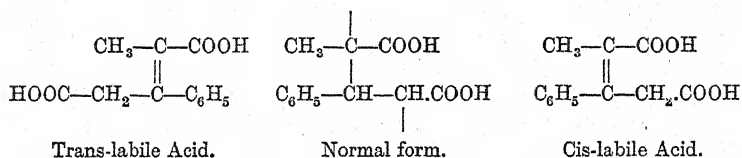
<sup>1</sup> Thole and Thorpe, *J.*, 1911, 99, 2187, 2208; Bland and Thorpe, *J.*, 1912, 101, 856, 871, 1490, 1557; Thorpe and Wood, *J.*, 1913, 103, 1579, 1752; compare Thorpe and Ingold's *Report on Some New Aspects of Tautomerism*, published by the Union Internationale de Chimie Pure et Appliquée.

wherein the hydrogen atom printed in heavy type is regarded as a mobile atom in equilibrium between the two unsaturated carbon atoms—a return to Laar's views on tautomerism. If the formula be written with free valencies as a stereo-formula, it is assumed to take the following shape :



which corresponds to a *meso*-form.

Now if this view be correct, then theoretically an acid of the glutaconic series should exist in three modifications: a *cis*-form, a *trans*-form, and a normal form indicated by the free-valency structure shown above. In practice,  $\beta$ -phenyl- $\alpha$ -methylglutaconic acid has actually been obtained in three forms to which the following formulæ have been ascribed :



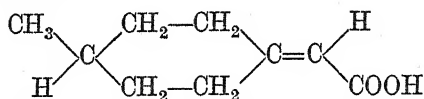
These results have led to interesting investigations on the problem of three-carbon systems by Thorpe, Ingold, and others; but space will not permit of any further examination of the subject in this place.

At this point something must be said about the progress of stereochemistry\*; for after a period of comparative quiescence, this branch of the subject began again to develop rapidly into fresh fields; and even in recent times new discoveries have shown that it is by no means an exhausted vein of research.

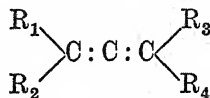
\* For a general account of this subject, Stewart's *Stereochemistry* may be consulted.

In 1899 the only two elements known to be capable of forming asymmetric centres of optical activity were carbon and nitrogen; but since then the list has been greatly increased by the addition of sulphur,<sup>1</sup> selenium,<sup>2</sup> tin,<sup>3</sup> silicon,<sup>4</sup> phosphorus,<sup>5</sup> arsenic,<sup>6</sup> cobalt,<sup>7</sup> chromium,<sup>8</sup> rhodium,<sup>9</sup> and iron.<sup>10</sup>

The whole question of molecular symmetry was raised by a paper of Perkin, Pope and Wallach<sup>11</sup> describing the resolution into optically active components of an acid having the following structure:—



It will be recalled that in one of his earliest publications on stereochemistry, van't Hoff pointed out that optical activity might be expected in compounds of the type:



owing to the fact that, although there is no asymmetric carbon atom in the molecule, the groups  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_4$  are tetrahedrally grouped in space, as can easily be seen by considering the arrangements of bonds around the central carbon atom on the van't Hoff hypothesis. The one double bond lies in the plane of the paper, whilst the other must be at right angles to the paper; and hence a similar grouping of  $\text{R}_1$  and  $\text{R}_2$  in the plane of the paper and  $\text{R}_3$  and  $\text{R}_4$  above and below the plane of the paper must exist. The cyclic compound shown above belongs to the same type, since in its case the ring takes the place of one of the double bonds.

<sup>1</sup> Smiles, *J.*, 1900, 77, 1174; Pope and Peachey, *ibid.*, 1072; Phillips, *J.*, 1925, 127, 2552.

<sup>2</sup> Pope and Neville, *J.*, 1900, 81, 1552.

<sup>3</sup> Pope and Peachey, *P.*, 1900, 16, 42, 116.

<sup>4</sup> Kipping, *J.*, 1907, 91, 209.

<sup>5</sup> Kipping and Challenger, *J.*, 1911, 99, 626; Meisenheimer and Lichtenstadt, *Ber.*, 1911, 44, 356.

<sup>6</sup> Mills and Raper, *J.*, 1925, 127, 2479; compare Burrows and Turner, *J.*, 1921, 119, 426.

<sup>7</sup> Werner, *Ber.*, 1911, 44, 1887.

<sup>8</sup> *Ibid.*, 3231.

<sup>9</sup> *Ibid.*, 1912, 45, 1228.

<sup>10</sup> *Ibid.*, 433.

<sup>11</sup> Perkin, Pope and Wallach, *J.*, 1909, 95, 1785; compare Perkin and Pope, *J.*, 1911, 99, 1510; Mann and Pope, *J. Soc. Chem. Ind.*, 1925, 44, 833.

The claim that this substance contained no asymmetric carbon atom was contested<sup>1</sup> on the ground that the carbon atom carrying the methyl group is really asymmetrical if the structure of the rest of the molecule be taken into consideration. The matter seems to be one depending upon the interpretation given to the term "asymmetric carbon atom"; and the reader may form his own judgment on the question.

New methods of resolving racemic compounds into their antipodes have been devised. Some of these present nothing essentially novel in conception.<sup>2</sup>

Much more original was the method devised by Marckwald and Meth,<sup>3</sup> which depends upon the difference in rapidity of amide formation between an active amine and the *d*- and *l*-forms of an active acid. Thus when racemic mandelic acid was heated with lævo-menthylamine, it was found that the acid left unacted upon after the process had gone on for ten hours was optically active. This method is based on the same line of reasoning as the method of Marckwald and McKenzie,<sup>4</sup> who showed that when racemic mandelic acid is esterified with menthol the reaction between the menthol and the *d*-form is more rapid than is the case with the *l*-acid; so that by interrupting the process before the acid is completely esterified the residual acid is optically active.

A fresh field was opened up by Marckwald<sup>5</sup> in the accomplishment of the first asymmetric synthesis of an optically active substance. In an asymmetric synthesis, an optically active compound is taken as the starting-point. To this an extra radicle is added, so as to form a new asymmetric carbon atom. The original optically active portion of the molecule is then split off; and if the synthesis is successful, the remainder of the substance, containing the new asymmetric carbon atom, will be optically active. For example, Marckwald utilized methyl-ethyl-malonic acid (I.) which contains no asymmetric carbon atom. He combined this with optically active brucine, thus introducing asymmetry into the molecule (II.). Now on heating this compound, carbon dioxide is split off forming

<sup>1</sup> Everest, *Chem. News*, 1909, 100, 295; *P.*, 1911, 27, 285; Marsh, *P.*, 1911, 27, 317; Smith, *J. Soc. Chem. Ind.*, 1925, 44, 1107.

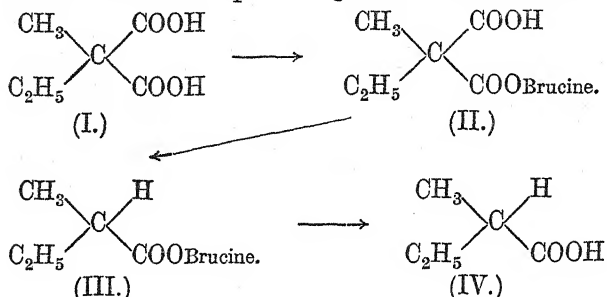
<sup>2</sup> Erlenmeyer, jun., *Ber.*, 1903, 36, 976; Neuberg, *Ber.*, 1903, 36, 1192.

<sup>3</sup> Marckwald and Meth, *Ber.*, 1905, 38, 801.

<sup>4</sup> Marckwald and McKenzie, *Ber.*, 1899, 32, 2130.

<sup>5</sup> Marckwald, *Ber.*, 1904, 37, 349, 1368, 4696.

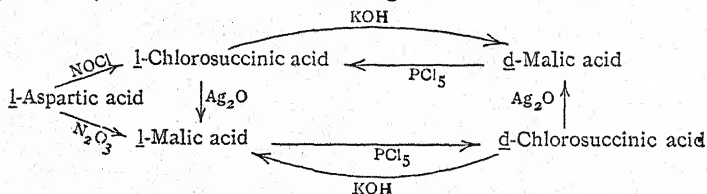
(III.), a compound which contains a new asymmetric carbon atom. Under the influence of the active brucine, a preference is given to one active form over the other during this process; and when the brucine is split off again, the acid remaining (IV.)



is found to be optically active.

In the whole field of stereochemistry no more puzzling phenomena are known than those grouped under the head of the Walden Inversion; and at the present day we still await a solution of the problem. The data are so complicated that it would be impossible to deal with them fully here: all that can be done is to indicate the nature of the question.<sup>1</sup>

Walden<sup>2</sup> observed that when certain optically active compounds were treated with non-asymmetrical reagents the sign of the rotatory power was altered in some cases, dextro-compounds being converted into lævo-isomers without any marked racemization being observed. The following scheme shows some of these conversions; and it will be seen that lævo-malic acid, for instance, can be changed into dextro-malic acid by the successive use of phosphorus pentachloride and silver oxide; whilst the converse change of dextro-malic acid into the lævo-isomer can be accomplished by the use of the same reagents in the same order:

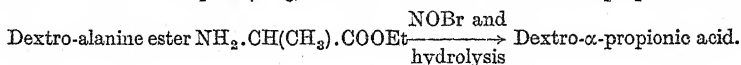
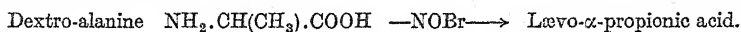


<sup>1</sup> For further details and references, see *Ann. Reports*, 1911, 1912, 1926, 1929, and Stewart, *Stereochemistry* (2nd edition).

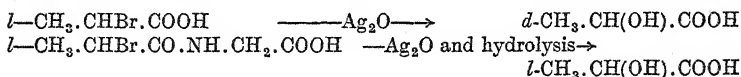
<sup>2</sup> Walden, *Ber.*, 1893, 26, 213; 1895, 28, 1287, 2771; 1897, 30, 3146; 1899 32, 1833, 1855.



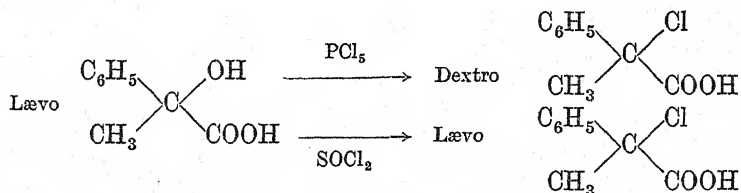
Another mysterious case is that of dextro-alanine and its ester.<sup>1</sup> When *d*-alanine is treated with nitrosyl bromide, it produces *l*- $\alpha$ -bromopropionic acid; whilst *d*-alanine ester, when subjected to the action of nitrosyl bromide and subsequent hydrolysis, yields the corresponding antipode, *d*- $\alpha$ -bromopropionic acid:



Again, when silver oxide acts upon an  $\alpha$ -halogen fatty acid and upon the product obtained by coupling this acid with glycine,<sup>2</sup> the results are optically different:



The case of *l*- $\alpha$ -hydroxy- $\alpha$ -phenylpropionic acid is interesting.<sup>3</sup> When this substance is treated with phosphorus pentachloride it yields a *d*-chloro-acid; whilst when thionyl chloride is used, there is no change of rotatory power, the *l*-chloro-acid being formed:



Senter and his collaborators<sup>4</sup> have thrown light upon the matter from a different direction by examining the influence of the solvent on the course of the reaction. In the case of optically active bromophenylacetic acid,  $\text{C}_6\text{H}_5\cdot\text{CHBr}\cdot\text{COOH}$ , they have shown that if this be allowed to react with ammonia in aqueous or alcoholic solution, the amino-acid formed has a sign opposite to that of the original bromo-compound: whilst

<sup>1</sup> Fischer, *Ber.*, 1907, 40, 489.

<sup>2</sup> *Ibid.*, 502; Fischer and Raske, *ibid.*, 1052; Fischer and Schoeller, *Annalen*, 1907, 367, 11.

<sup>3</sup> McKenzie and Clough, *J.*, 1910, 97, 1016, 2566.

<sup>4</sup> Senter and Drew, *J.*, 1915, 107, 638; 1916, 109, 1091; Senter and Tucker, *J.*, 1918, 113, 140; Senter, Drew, and Martin, *ibid.*, 151.

if the solvent be liquid ammonia or acetonitrile, the sign of the rotatory power is not reversed by the reaction. Imino-diphenyl-acetic acid is formed to some extent during the reaction. When  $\alpha$ -bromo- $\beta$ -phenylpropionic acid,  $C_6H_5 \cdot CH_2 \cdot CHBr \cdot COOH$ , is treated with ammonia in various solvents, some cinnamic acid is always produced.

Finally, the amine oxide containing pentavalent nitrogen may be mentioned. Compounds of the type methyl ethyl aniline oxide  $(CH_3)(C_2H_5)(C_6H_5)N : O$  can be resolved into two optically active isomers in spite of the presence of doubly bound oxygen in the molecule.<sup>1</sup> It is well known that the five nitrogen valencies in ammonium compounds are not all equal, the valency holding an ionizable group being considered to occupy a unique position. In the amine oxides containing three different radicles it is assumed that one of the oxygen bonds is that which previously held an ionizable group.

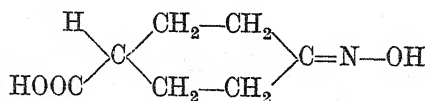
One of the most complicated problems in the stereochemical field is that which concerns the numerical value of optical rotatory power. Two subsidiary questions are here involved: first, the influence of the active compound's structure; and second, the effect of the solvent in which it may be dissolved. With regard to the first of these we are still apparently far from any satisfactory conclusion, though many facts have been accumulated by various investigators. Certain rough generalizations with regard to the effect of introducing double or triple bonds in place of single linkages have been made; but we are still far from the time when it may be possible to assess the approximate numerical value of the rotatory power from an examination of the active compound's constitution, as we can do in the case of refractive indices.

With regard to spatial relations which do not produce optical activity, the most far-reaching work is that of Bragg on the X-ray examination of crystal structure; but it would lead us too far if we were to attempt to summarize his results here.

The Hantzsch-Werner theory of *cis-trans*-isomerism in the oximes has been put to a crucial test from which it has emerged intact. Examination of the formula of the oxime of cyclohexanone-4-carboxylic acid, which is shown below, will reveal

<sup>1</sup> Meisenheimer, *Ber.*, 1908, 41, 3966; *Annalen*, 1911, 385, 117; 1913, 397, 273; 399, 371; 1922, 428, 252; 1926, 449, 191.

at once that this structure is a symmetrical one if the oximic hydroxyl group lies in a straight line with the axis of the  $\text{—C=N—}$  bond.



On the other hand, if the oximic hydroxyl group lies to one side or other of the axis of the  $\text{—C=N—}$  bond (as is demanded by the Hantzsch-Werner theory), then the molecule becomes centro-asymmetrical and should be obtainable in optically active forms. A resolution of this acid into its optical antipodes was carried out successfully by Mills and Bain<sup>1</sup>; and thus the Hantzsch-Werner theory has received its most striking confirmation. Simultaneously, however, grave doubt has been thrown<sup>2</sup> on the applicability of some of the methods hitherto used in the determination of the configurations of the oximes.

In 1885, Baeyer<sup>3</sup> put forward his well-known Strain Theory based upon the assumption that the valencies of a carbon atom normally acted at angles of  $109^\circ 28'$  with each other but could be diverted during the formation of rings; and that the deviation required to form the cyclic grouping was a measure of the difficulty of forming the ring-compound.<sup>4</sup> Since substitution is known to have marked influence on the stability of rings,<sup>5</sup> it was evident that it also was a factor in stability questions. An important study of this field has been carried out by Thorpe and his collaborators.<sup>6</sup> The data furnished by them are far

<sup>1</sup> Mills and Bain, *J.*, 1910, 97, 1866; see also Mills and Schindler, *J.*, 1923, 123, 212.

<sup>2</sup> Bucherer, *Lehrbuch d. Farbenchemie*, p. 202 (1914); Meisenheimer, *Ber.*, 1921, 54, 3206; Meisenheimer and Meis, *Ber.*, 1924, 57, 289; Auwers and others, *Ber.*, 1924, 57, 446, 800; 1925, 58, 26, 36; Brady and Bishop, *J.*, 1925, 127, 1357; Beckmann and others, *Ber.*, 1923, 56, 341; Meisenheimer and others, *Annalen*, 1925, 444, 94; Kuhn and Abel, *Ber.*, 1925, 58, 919, 2088; Boeseken, *Ber.*, 1925, 58, 1470.

<sup>3</sup> Baeyer, *Ber.*, 1885, 18, 2277.

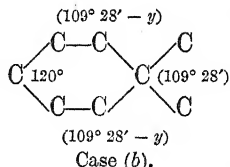
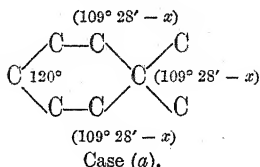
<sup>4</sup> For some account of the application of the Strain Theory, see Stewart, *Stereochemistry*, p. 175 (1919).

<sup>5</sup> See Stewart, *Stereochemistry*, p. 203 (1919).

<sup>6</sup> Beesley, Ingold and Thorpe, *J.*, 1915, 107, 1080; Ingold and Thorpe, *J.*, 1919, 115, 320; Becker and Thorpe, *J.*, 1920, 117, 1579; Kon, *J.*, 1921, 119, 810; compare Kenner and Turner, *J.*, 1911, 99, 2101; Kenner, *J.*, 1914, 105, 2685; Ingold, *J.*, 1921, 119, 305.

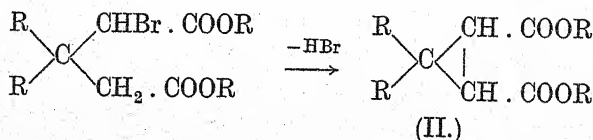
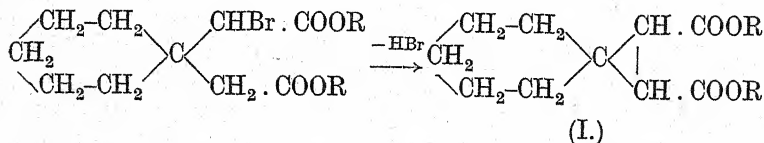
too voluminous to discuss adequately even in a chapter, so only a brief account can be given of the results obtained.

The normal angle made by the sides of a hexagon is  $120^\circ$ ; so that in order to form the ring-compound shown below, two valencies of the quaternary carbon atom must be diverted from their normal position.



The remaining two valencies of the quaternary carbon atom\* might then be supposed either (a) to distribute themselves evenly in space as indicated in Case (a) above, or (b) to remain at the normal tetrahedral angle of  $109^\circ 28'$ , as shown in Case (b). Inspection will show at once that in Case (a) the two carbon atoms external to the ring will be nearer together than they would be in Case (b), where the normal angle is maintained.

Now in an open-chain compound, the angles may be assumed to be  $109^\circ 28'$ . Therefore by comparing the behaviour of an open-chain compound with that of a cyclic compound, it should be possible to determine which of the two views is correct. For example, if affairs are correctly represented by Case (a), then there should be a greater tendency to form the *spiro*-compound (I.) below than there is to form the analogous open-chain compound (II.); whereas if Case (b) represents the true state of things, then the removal of hydrogen bromide should be equally easy in both reactions.

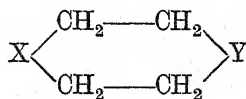


\* Those attached to the two carbon atoms not forming part of the ring.

Examination of a large number of examples has now shown that the *spiro*-compound is much more readily formed than the open-chain one, which indicates that Case (a) represents the state of affairs better than Case (b); and this is confirmed by the study of the relative stabilities of the fresh rings in the molecule.

Another problem which attracted a certain amount of attention is concerned with what has been termed spatial conjugation. It will be recalled that on the hypothesis of the tetrahedral arrangement of groups around the carbon atom, the first carbon atom in a straight chain may approximate closely in space to the fifth and sixth atoms of the chain. Similarly it is assumed on account of various reactions that the 1 : 4 positions of a six-membered cyclic compound may also be in some way closely related to each other. From an examination of optically active salts and esters of dicarboxylic acids in which the carboxyl radicles lay at opposite ends of the chain, Hilditch<sup>1</sup> showed that when these groups were situated in the 1 : 5 or 1 : 6 positions with regard to one another, anomalous rotatory powers were observed; from which it follows that the groups must have influenced one another owing to their proximity in space, since structurally they are far removed from each other.

The same problem was attacked in a different way by Clarke.<sup>2</sup> He measured the reactivity of atoms in the positions X and Y in the formula below, wherein X and Y may be =NR, —O— and —S—. All possible combinations of these groups in pairs were investigated :—



It was found that when X and Y are atoms capable of raising their valency (for example : divalent sulphur, which can become quadrivalent, or trivalent nitrogen, which can show penta-valence) and may therefore be supposed to be capable of exhibiting residual affinity, the two atoms X and Y do actually influence each other's reactivities. Further, if X and Y be identical, their reactive power is increased; whereas if X and Y be different (for example X=S and Y=O), their activity is diminished.

A fresh aspect of the question is disclosed when the

<sup>1</sup> Hilditch, *J.*, 1909, 95, 1578.

<sup>2</sup> Clarke, *J.*, 1912, 101, 1788.

absorption spectra of stereoisomerides are examined.<sup>1</sup> Since these compounds are structurally identical, the difference in their absorptive power must be ascribed to purely spatial influences. It was found that the difference between the absorption spectra of two isomerides was greatest when the change from one form to the other entailed the relative shifting in space of two unsaturated radicles. When this condition was not present the differences observed were slight.

These pieces of evidence, drawn from such widely differing fields, certainly point to the probability that spatial conjugation is a factor which may play a marked part in certain cases.

The application of X-ray diffraction methods to the study of natural materials has led to interesting results and has markedly extended our knowledge of the structures of fibres<sup>2</sup> such as ramie, rubber, hair, silk, and wool. The method employed is to send a fine X-ray pencil lengthwise through a bundle of parallel fibres and to photograph the diffraction pattern thus obtained.

Three main conclusions have been drawn from the results. Fibres may be constructed from molecular chains of fairly simple chemical units, which are linked, fore and aft, by ordinary valencies. A bundle of these chains goes to form a long, thin, sub-microscopic micelle or crystallite; and these crystallites may lie with their long axes parallel to the axis of the fibre itself (as in the case in ramie, hair, silk, and wool)-or may have their axes inclined at a constant angle to the axis of the fibre (as in cotton fibre). Some fibres, like those of cellulose, silk, stretched rubber and stretched hair, may consist of extended molecular chains. Others, like unstretched rubber and unstretched hair, may contain folded molecular chains. If the stretching process be carried to the furthest extent obtainable by unfolding the "curled-up" molecular chains in the fibre, there still remains the possibility that the unfolded chains may "re-curl" when the pull on the fibre is removed; and in this case the structure contracts and resumes its original architecture. But if the unfolding has been carried to its full possible extent, there is a further possible mode of lengthening, which takes place by an internal slipping among the units of the structure. This last

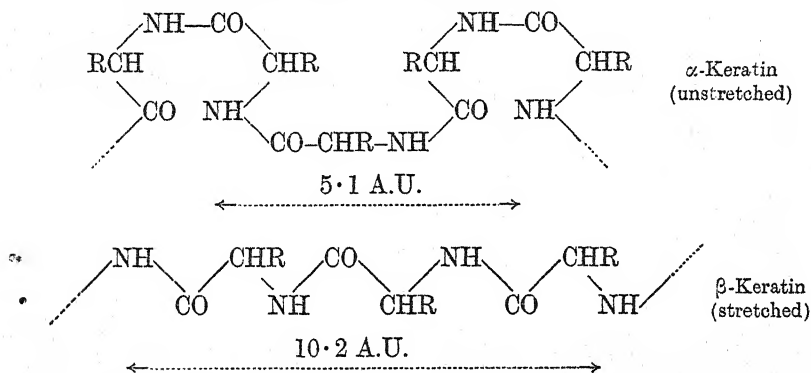
<sup>1</sup> Macbeth, Stewart, and Wright, *J.*, 1912, 101, 599.

<sup>2</sup> For an account of the earlier work in this field, see Astbury, *Fundamentals of Fibre Structure* (1933).



process is not reversible like the "re-curling" of the molecular chain; so that fibres thus stretched do not recover their original shorter length but remain extended.

Let us take the case of natural animal hair. This is built up from the protein  $\alpha$ -keratin and when it is stretched the structure extends by the unfolding of the molecular units and yields the  $\beta$ -keratin arrangement, as shown below. The two forms of keratin, ( $\alpha$  and  $\beta$ ), have the same chemical structure and differ only in their stereochemical arrangements.



Even the normal form of  $\alpha$ -keratin, present in ordinary hairs, does not represent the maximum possible contraction of the system; for it appears that a shrinkage of 50% can be obtained.<sup>1</sup>

Thus hair fibre can be reduced to half its normal length or extended to twice its normal length without dislocation of its chemical structure: a behaviour which brings it into the same class as indiarubber so far as this quality goes. Further, if a stretched hair be exposed to the action of steam, it loses its normal power of contraction and remains in the extended condition. This phenomenon is the basis of the "permanent wave" of the hairdresser; and wool fibres also acquire a "permanent set" under similar treatment.

Application of the X-ray diffraction method to feathers and scales has led to results which bear upon the theory of evolution. The fossil archæopteryx, the oldest known bird, had claws on its wings, teeth in its jaws, and a lizard-like tail of twenty vertebrae, each giving rise to a quill feather. It thus combined in

<sup>1</sup> Astbury and Street, *Phil. Trans.*, 1931, [A], 230, 75; Astbury and Woods, *Nature*, 1930, 126, 913.



itself the characteristics of a bird and a reptile; and it is assumed to represent a link between the two. Until quite recent times it was assumed that the "keratin" of feathers and scales was similar to the "keratin" of hairs. But X-ray diffraction methods<sup>1</sup> have now established that goose-quills and tortoiseshell give identical patterns which are entirely different from those obtained from animal hairs. This, in a most unexpected way, has confirmed the evidence from palæontology which established the natural kinship of the reptiles with the birds. It would be of considerable interest to know what results can be obtained from the keratin of the platypus.

We now come to a subject which lies in the borderland between organic and physical chemistry, namely, the relations between the physical properties of compounds and their chemical structure.<sup>2</sup> The problems comprised in this branch have, for the most part, been solved by organic chemists, owing to the fact that the material of experiment is largely drawn from the carbon compounds. The curious step-motherly fashion in which this important subject has been treated by the ordinary physical chemist is possibly due to the influence of Ostwald, who had a large following among the older group of physical chemists; or it may be ascribed to the fact that few physical chemists have any claim to be ranked as even moderate organic chemists, a fact which handicaps them in this particular line of research. Whatever be the reason, there is no doubt that the relations between chemical constitution and physical properties, so fully recognized by van't Hoff, have not been pursued with either eagerness or success by the physical chemists of the Ostwald school.

Specific heat, boiling-point, and melting-point have occupied less attention in recent years. The influence of chemical structure upon viscosity has furnished a subject for a number of workers, among whom Dunstan and his collaborators have been the most successful. The relations between volume and valency have formed the basis of a considerable amount of ingenious speculation by Traube, Barlow, Pope, and Le Bas.

<sup>1</sup> Marwick, *J. Text. Sci.*, 1931, 4, 31.

<sup>2</sup> For a complete account of this field up to 1910, the reader should consult Smiles' *Relations between Chemical Constitution and some Physical Properties*. Even a cursory perusal of the book will suggest many subjects for further investigation. See also Kauffmann, *Beziehungen zwischen physikalischen Eigenschaften und chemischer Konstitution* (1920).

The physical properties of a molecule may be regarded from either of two different standpoints: for we may assume the molecular properties to be merely the sum of the properties of the various atoms in the molecule; or we may decide to lay most weight upon the structural character of the compound. Unfortunately, this mode of classification breaks down at certain points; for it is found that in the case of some substances the properties of the molecule are apparently compounded partly from purely additive factors and partly from constitutive effects. A certain physical property may be traced as an additive factor throughout a whole series of compounds, and then may finally be so greatly influenced by constitutive factors that the value deduced from additive methods diverges widely from the result of experiment upon the next member of the series. Thus when we speak of additive and constitutive properties we mean merely that in the one case the additive factor is predominant, whilst in the second case the influence of constitution outweighs the purely additive effects.

An example of this is furnished by a relationship which has been detected between surface tension, density, and chemical composition. Macleod<sup>1</sup> discovered that a relation existed between the density and surface tension of substances which could be expressed in the equation:—

$$\gamma = C(D - d)^4$$

Here  $\gamma$  is the surface tension,  $D$  the density of the substance as liquid, and  $d$  its vapour density, all at the same temperature;  $C$  is a characteristic constant, independent of temperature, in the case of non-associated substances.

Sugden<sup>2</sup> showed that this relationship of Macleod's could be brought into direct touch with chemistry by a simple modification. Taking the fourth root on each side of the equation and multiplying them by  $M$ , the molecular weight of the substance under examination, the following relation is obtained:—

$$M\sqrt[4]{C} = \frac{M\sqrt[4]{\gamma}}{(D - d)} = \text{Parachor}$$

The function  $M\sqrt[4]{C}$  is termed by Sugden the parachor of the substance.

<sup>1</sup> Macleod, *Trans. Faraday Soc.*, 1923, 19, 38.

<sup>2</sup> Sugden, *J.*, 1924, 125, 1177.

It is self-evident that when a weight is divided by a density, the quotient represents a volume; and if, in this case, measurements are made at low temperatures (when  $d$  becomes very small) the factor  $M/(D-d)$  is simply the molecular volume of the substance under the experimental conditions.

The parachor, then, is the molecular volume of the substance multiplied by the factor  $\sqrt[4]{\gamma}$ . But this factor represents a measure of the surface tension of the liquid, and the surface tension is a measure of the internal pressure of the material. So, by comparing the parachors of two substances under conditions which make their surface tensions equal, we have a means of comparing their molecular volumes under equal internal pressures.\*

When the parachors of a large number of compounds were determined, it was found that the property is mainly an additive one; and the following constants were calculated in the usual manner:—

C = 4.8	Cl = 54.3	Double bond C : C = 23.2
H = 17.1	Br = 68.0	O <sub>2</sub> in esters = 60.0
O = 20.0	I = 91.0	6-membered ring = 6.1

One or two examples will show how close is the agreement between the calculated and the experimental results.

Ethylene bromide	<i>n</i> -Propyl formate
C <sub>2</sub> = $4.8 \times 2 = 9.6$	C <sub>4</sub> = $4.8 \times 4 = 19.2$
H <sub>4</sub> = $17.1 \times 4 = 68.4$	H <sub>8</sub> = $17.1 \times 8 = 136.8$
Br <sub>2</sub> = $68.0 \times 2 = 136.0$	O <sub>2</sub> = 60 = 60
Calculated = 214.0	Calculated = 216.0
Experiment = 215.1	Experiment = 216.1

Benzene (Kekulé formula)
C <sub>6</sub> = $4.8 \times 6 = 28.8$
H <sub>6</sub> = $17.1 \times 6 = 102.6$
3 Double bonds = $23.2 \times 3 = 69.6$
6-membered ring = 6.1 = 6.1
Calculated = 207.1
Experiment = 206.3

Further investigation revealed that the parachor, though mainly additive, is in certain cases influenced by constitution. One example of this will suffice here.

\* For water at ordinary temperatures the internal pressure is of the order of 11,000 atmospheres.

It appears that a distinction must be drawn between two kinds of double bonds: the non-polar and the semi-polar.<sup>1</sup> The former adds 23.2 units to the parachor, whilst the latter lowers the parachor value by 1.6 units. On the electronic theory of valency,\* the non-polar double bond is supposed to be produced by two co-valencies, whilst the semi-polar bond is assumed to consist of one co-valency and one electrovalency. Langmuir assumed that double bonds between carbon atoms were of the non-polar type; and Sugden<sup>2</sup> has suggested that there is free rotation in the case of semi-polar double bonds. An examination of the parachors in the maleic-fumaric acid series proved that there the double bonds had parachoric values corresponding to the non-polar type, which fits in neatly with the cis-trans isomerism characteristic of the series.

From facts such as these it is evident that even in the case of a markedly additive property, constitutional factors make their appearance in the problem. Another example of the same kind may be found in the refractive indices of compounds. In the case of saturated molecules or unsaturated compounds containing centres of residual affinity which are isolated from each other, the refractive power of the substances can be calculated with extraordinary accuracy by simply adding together the pre-determined constants of the atoms which go to form the molecule. But if the structure contains a conjugated system of double bonds, the refractivity becomes anomalous and cannot be calculated on an additive basis. In this case, it is evident that constitutive influences are overbearing the purely additive relationship.

This peculiar influence of conjugation makes itself apparent in nearly all optical properties. Magnetic rotatory power—*i.e.* the property of rotating the plane of polarization which is acquired by symmetrical substances when placed in a magnetic field—is calculable, in the main, so long as no conjugation is present in the molecular structure; but substances containing conjugated double bonds are found to exhibit a certain "exaltation" above the calculated value; so that, here also, the constitutional factor outweighs the purely additive effects.

<sup>1</sup> Sugden, Reed, and Wilkins, *J.*, 1925, 127, 1525; Sugden and Whittaker, *ibid.*, 1868.

\* See Chapter XVI., Vol. III.

<sup>2</sup> Sugden, *J.*, 1923, 123, 1864.

When absorption spectra are examined, it is found that the manner in which the atoms are linked in the molecule may exert far more influence than the nature of the atoms themselves. At the beginning of the century, this subject attracted very wide interest, either in the crude form of "relations between colour and constitution," or in the more accurate survey of the visible and ultra-violet regions by the aid of the quartz spectrograph. The invention of the sector photometer by Henri for the determination of extinction coefficients in the ultra-violet marked a great stride forward in accuracy of method; and Henri<sup>1</sup> has been enabled to calculate graphs of the absorptive power of certain substances.

In the spectroscopic branch an entirely new field was opened up by McVicker, Marsh, and Stewart<sup>2</sup> through the discovery of the Tesla-luminescence spectra. In earlier years, the only emission spectra obtainable were those of the elements or of comparatively few stable compounds such as carbon monoxide and carbon dioxide. By using the high-tension Tesla discharge, it is now possible to photograph the emission spectra of highly complex compounds such as benzene and its derivatives; and the extraordinary regularity of the benzene spectrum seems to suggest that through it mathematics may be brought to bear upon some of the fundamental problems of organic chemistry. The Tesla-luminescence spectra are constitutive in character, each class of compound having its own general spectral type. Curiously enough, the influence of conjugation appears to be very small so far as this physical property is concerned.

Fluorescence is another property in which constitutive relations play a preponderant part. So far as visible fluorescence is concerned, Hewitt's theory of double symmetrical tautomerism<sup>3</sup> appears to be the most successful attempt yet made to discover the factors underlying the phenomena. Recent work<sup>4</sup> on the fluorescence of substances in the vapour state, however, suggests that the problem as a whole is by no means easy to solve.

<sup>1</sup> Henri, *Etudes de photochimie* (1919).

<sup>2</sup> McVicker, Marsh, and Stewart, *J.*, 1923, 123, 642, 2147; 1924, 125, 1743; 1925, 127, 999; 1926, 129, 17; *Phil. Mag.*, 1924, 48, 628; *J. Amer. Chem. Soc.*, 1924, 46, 1351; MacMaster, Russell and Stewart, *J.*, 1929, 2401; Russell and Stewart, *J.*, 1929, 2407, 2432.

<sup>3</sup> Hewitt, *Z. physikal. Chem.*, 1900, 34, 1; *J. Soc. Chem. Ind.*, 1903, 22, 127.

<sup>4</sup> McVicker and Marsh, *J.*, 1923, 123, 820; Marsh, *ibid.*, 3315; 1924, 125, 418; Numan and Marsh, *ibid.*, 2123; Marsh, *Phil. Mag.*, 1925, 49, 971, 1206.

Magnetic susceptibility,<sup>1</sup> when studied from the constitutional standpoint, is found to resemble magnetic rotation in character, being influenced partly by additive factors and partly by the general constitution of the molecule.

Electrical double refraction<sup>2</sup> and dielectric constant<sup>3</sup> have also been worked upon; but they appear to be so highly constitutive in character that only the most general inferences can be drawn from the experimental results.

One of the most highly constitutive properties yet discovered is anomalous electric absorption<sup>4</sup> which seems, so far as our present information goes, to be almost entirely restricted to compounds containing hydroxyl groups.

From the foregoing paragraphs it will be seen that an immense amount of research remains to be done upon the connection between physical properties and chemical structure. We still await some general theory which will co-ordinate the various branches of the subject. From a survey of the data at present available, it seems clear that the more purely electrical a property is, the more does the influence of constitution preponderate. Thus refractive index is largely additive; magnetic rotation and magnetic susceptibility are slightly more constitutive in character; anomalous electric absorption and electrical double refraction are almost entirely constitutive; while the Tesla-luminescence spectra appear to be entirely constitutional properties. It is true that absorption spectra form an apparent exception to this rule.

The conception of intramolecular change is far from new. It appears as far back as the day when Wöhler established the conversion of ammonium cyanate into urea and thus broke down the existing barrier between inorganic and organic chemistry. Later, it re-appears in Kekulé's vibrational formula for benzene. Later still, it furnished a battle-ground in the long-contested problem of acetoacetic ester's constitution.

An adumbration of modern views appeared near the beginning

<sup>1</sup> Pascal, *Bull. soc. chim.*, 1909 (iv), 5, 1110.

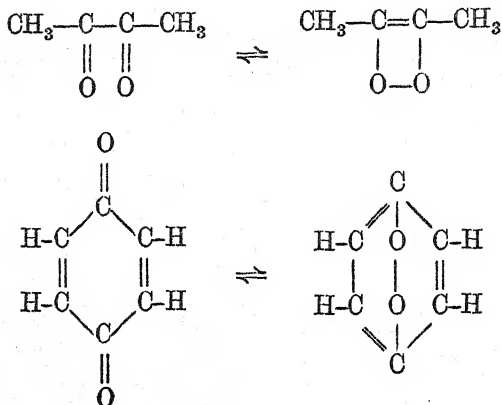
<sup>2</sup> Cotton and Mouton, *Ann. Chim. Phys.* (viii), 1907, 11, 145; 1910, 19, 153; 20, 153, 194; 1913, 28, 209.

<sup>3</sup> Drude, *Z. physikal. Chem.*, 1897, 23, 309; Walden, *ibid.*, 1903, 46, 176; 1906, 54, 139; 1910, 70, 584.

<sup>4</sup> Drude, *Z. physikal. Chem.*, 1902, 40, 635; compare Walden, *ibid.*, 1903, 46, 176.



of the present century. In order to account for certain peculiarities in the absorption spectra of  $\alpha$ -diketones and quinones, Stewart and Baly<sup>1</sup> suggested that molecules of these types were in a state of constant vibration, the extreme phases of which could be represented by formulæ like :—



Measurements of the reactivities of such compounds led to the idea that the passage from one extreme phase to the other might account for the high degree of reactivity which they show. These views were put forward before modern electronic formulæ had been devised ; and at that date it was impossible to carry the suggestion further with any success.

The quantum theory made a fresh advance possible. According to wave-mechanics, the state of a stable molecule can be represented by a function,  $\psi$ . Some molecules, however, are capable of existing in two forms, A and B, in which the electronic grouping of A is different from that existing in B. In the case of A, the function may have the value  $\psi_1$  ; whilst in the case of B, it may have the value  $\psi_2$ . In any given specimen of the substance, a certain number of the molecules will be present in the A-form and a certain number in the B-form. Now let  $a$  represent the probability that a given molecule is in the A-form at a given moment, whilst  $b$  represents the probability that it exists in the B-form at that instant ; then according to wave-mechanics the state of the system can be expressed by the linear

<sup>1</sup> Stewart and Baly, *J.*, 1906, 89, 489.

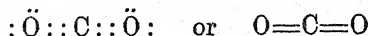


combination:  $a\psi_1 + b\psi_2$ . Here  $a$  and  $b$  vary with time; and when this is interpreted, it means that the molecule must be regarded either as changing from A to B (and *vice versa*) with very high frequency, or else as having a structure which lies intermediate between A and B and which can hardly be expressed by our ordinary structural formulæ. The process of change is termed resonance.<sup>1</sup>

Resonance is supposed to occur only when two conditions are fulfilled. In the first place, the atoms in the two systems must occupy practically similar positions; or, in other words, both systems must have the same structural formula. Secondly, the energy contents of the two systems must be approximately equal. As the frequency of the change from one form into the other is assumed to be about  $10^{15}$  times per second, it is plain that the only moving objects concerned must be electrons, since no hydrogen atom could be expected to move with the necessary speed.

If resonance be assumed to occur in a substance, there should be three main results. First, the substance should exhibit the properties of both the possible structures, but the properties of the form with the greater energy content and smaller stability will be less prominent than those of the other form. Secondly, the distances between the atoms of either structure should be less than the distances as calculated for a normal covalency. Thirdly, the heat of formation of the substance should be greater than that calculated for either of the alternative structures.

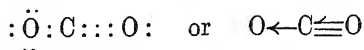
The case of carbon dioxide will serve to illustrate these points. The carbon dioxide molecule may be represented normally by three complete octets of electrons, wherein the central octet contains four electrons supplied by the carbon atom and a couple of pairs of electrons derived from the two oxygen atoms, each of which contributes a pair. We can symbolise this as shown below:



On the other hand, the three octets may be constituted by the

<sup>1</sup> Pauling, *J. Amer. Chem. Soc.*, 1931, 53, 3225; 1932, 54, 988, 3570; Pauling and Wheland, *J. Chem. Physics*, 1933, 1, 362; Pauling and Sherman, *ibid.*, 606, 679; Pauling, *Proc. Nat. Acad. Sci.*, 1932, 18, 293, 498; and later papers.

carbon atom donating two electrons to one of the oxygen atoms whilst the bond between it and the other oxygen atom is built up from a pair contributed by the carbon atom and four electrons contributed by the oxygen system :



(It is self-evident that the third possible arrangement,  $\text{O} \equiv \text{C} \rightarrow \text{O}$ , is identical with the one already shown.)

On comparing the observed values with the values calculated on the foregoing assumption for the atomic distances in Ångstrom units and the heats of formation of the two systems, the following result is obtained :

	O=C=O	O←C≡O	Observed
	1.23   1.28	1.43   1.13	
Distances . . . . .	2.56	2.56	2.30
Heats of formation, Kg. cal. . .	348	circa 350	380

It is clear that the actual atomic distances are much less than is calculated from the figures obtained from the carbonyl groups of aldehydes and ketones ; whilst the heat of formation of carbon dioxide in practice is much greater (about 30 Kg. cal.) than that calculated from the ketonic or aldehydic carbonyl group.

Photochemistry <sup>1</sup> has grown by leaps and bounds since the beginning of the century and is rapidly reaching the stage when it will be considered a subject in itself. The problems already presented by it are too numerous to be dealt with in this place ; although the fringe of the subject is all that has been attacked as yet.

The survey given in the previous pages of the progress of organic chemistry during the present century, though very incomplete, will suffice to indicate the main lines upon which work is proceeding at the present day ; and it should be sufficient to show that fresh subjects of research are still plentiful. The newer trend towards a study of natural products comes as a relief after the long supremacy of the purely synthetic work

<sup>1</sup> Accounts of the subject are given in Sheppard's *Photochemistry* (1914), and in Griffith and McKeown's *Photo Processes in Gaseous and Liquid Systems* (1929).

- of the late nineteenth century; and it may be emphasized in this place that in the near future the study of quite simple reactions will offer many points of interest. We are far too apt to be captivated by the application of old reactions to new syntheses; and it seems likely that more interesting and useful work could be carried out by an examination of even such obvious problems as the hydration and dehydration of simple organic compounds.

## CHAPTER II

### SOME CARBOHYDRATE CONSTITUTIONS

#### A.—INTRODUCTORY

AMONG organic compounds, the carbohydrate class occupies a unique position, since in one form or another its members have become almost indispensable to modern civilization. Sugar and starch occur in our foodstuffs. The growing plant's cell-walls are formed from cellulose, which is thus the keystone of agriculture. Cellulose in the form of wood finds applications as fuel, as a building material, and in the construction of furniture. It is the basis of the manufacture of cheap paper; it is an essential raw material in the making of cinema-films; and it is utilized in the making of many commercial explosives. On it, too, the cotton trade is founded; and the recent rise of artificial silk represents yet another field of application for the carbohydrates. Even in pathology this group has a marked importance, since glycogen forms a reserve supply of nutriment in the animal body, and glucose acts as a danger-signal in cases of diabetes.

On the chemical side, the study of the carbohydrate group is of considerable historical interest; for a narrative of it is found to fall naturally into successive chapters and to illustrate in an exceptionally striking manner the influence of new theories and fresh methods upon the progress of chemical science.

In the early days of organic chemistry, the sugars offered the greatest difficulties to investigators. Unguided by any clear ideas of chemical structure, the chemists who attacked the carbohydrate group had to content themselves with purely empirical and descriptive results; and the complexity of the subject must have disappointed many an eager investigator. A glance at the edition of Gmelin's *Handbuch der organischen Chemie* published in the middle of last century will reveal how chaotic the subject must have appeared at that time, even to the most expert. If research had closed at this point, our knowledge would have been confined to a series of facts, most

of which seemed to bear little relationship to one another and all of which appeared to lack any power of suggestion for a fresh start. Pure practice had failed to clarify the subject.

Then came the great days of the structural chemistry evolved by Kekulé, and a fresh light was thrown upon the whole field. Baeyer and Zincke were not slow to see the possible applications of constitutional ideas in the sugar group, and more or less modern formulations of the saccharides made their appearance. Almost on the heels of this came van't Hoff's extension of chemical formulæ into three dimensions; and with that advance the hitherto incomprehensible complexity of the carbohydrate problem began to fade out.

But even with all this, the riddle of the carbohydrates still had difficulties of its own: for the physical character of many members of the group offered resistance to the normal processes of purification; and the task of disentangling from each other a series of closely-similar materials presented practical stumbling-blocks which even the finest experimental skill could hardly surmount. Fischer's discovery of the phenylhydrazones and osazones was necessary before any real advance could be made. The utilization of phenylhydrazine, coupled with the application of the structural and stereochemical ideas which had come into vogue, produced a complete change in one aspect of the carbohydrate chemistry. In an almost incredibly short period, Fischer carried to a successful conclusion a vast research which ended with the determination of the structure and spatial configurations of all the known pentoses and hexoses. At one sweep, our knowledge of the monosaccharides had been extended, clarified, and consolidated.

With the close of Fischer's activity in this region of organic chemistry, the general interest in the carbohydrate group suffered what was, perhaps, a natural decline. In the special branch which he had attacked but little remained for subsequent investigators; and there was a quite comprehensible diffidence shown by other researchers in entering the field. Thus, for a time, the subject was studied, if at all, on a scale much more modest than that to which Fischer had accustomed our minds. The action of enzymes on various sugars was investigated and enzymatic syntheses were worked out; whilst further examination was made of the constitutions of various members of the

sugar group. But though much valuable information was thus acquired, the results lacked something which had illuminated the previous period. They formed a mass of valuable data, but behind them there was no single intellect concentrated on a huge problem and seeing it as a whole. Even the scientific mind is capable of appreciating the romantic side of science; and undoubtedly the picture of a single personality mastering a vast region of investigation produces a more definite impression than does the work of a group of independent investigators attacking a problem piecemeal. On the whole, then, this period of sugar chemistry suffered in interest by comparison with the brilliancy of the Fischer era; and for a time it seemed as though the carbohydrates had sunk back into obscurity, so far as the general interest of organic chemists was concerned.

The third period in the history of sugar chemistry opened almost simultaneously with the beginning of the present century. Fischer's researches had cleared up the field of the monosaccharides; but our knowledge of the polysaccharides was left in almost the same condition as it had been before he entered upon the study of the carbohydrates. The new attack was opened by Purdie and his collaborators. It seems desirable to sketch the main outlines of the succeeding campaign in this place, so as to lend some perspective to the details which will be given in later sections.

Like Fischer, the new investigators had armed themselves with a fresh weapon. As phenylhydrazone formation had been the key to the monosaccharides, so methylation was to throw light upon the constitutions of the much more complex carbohydrates. The attack was launched on a modest scale by the preparation of a crystalline tetramethyl-glucose.<sup>1</sup>

The methylation of sundry other members of the sugar group was rapidly taken in hand. Galactose,<sup>2</sup> sucrose, and maltose<sup>3</sup> were subjected to methylation; and in 1906 an extension of the method into a fresh region showed that the new process could be applied to determine the structure of the typical natural glucoside, salicin.<sup>4</sup>

<sup>1</sup> Purdie and Irvine, *J.*, 1903, 83, 1026.

<sup>2</sup> Irvine and Cameron, *J.*, 1904, 85, 1081.

<sup>3</sup> Purdie and Irvine, *J.*, 1905, 87, 1025.

<sup>4</sup> Irvine and Rose, *J.*, 1906, 89, 814.

In 1910, an entirely fresh field was entered by Denham and Woodhouse,<sup>1</sup> who applied a new method of methylation by means of which they were able to introduce methyl radicles into cellulose. Starch also came within the range of investigation about the same period.

A modification of the new methylation method enabled it to be applied to the preparation of glucosides and methylated glucosides<sup>2</sup>; and the simplification of work in such cases facilitated the constitutional study of sucrose, lactose, maltose, and cellobiose.<sup>3</sup>

The preparation of these numerous methylated carbohydrates, and the identification of the fission-products of the simpler polysaccharides after hydrolysis, represent in themselves a gigantic piece of work; but to see the matter in true perspective it must be borne in mind that all this labour was undertaken merely as a first step towards the solution of the most intricate problems in the carbohydrate field. Stage by stage, the investigation was consolidating the ground for the final attack upon the constitutions of the most complex naturally-occurring carbohydrates. One by one, the structures of the simpler materials were determined; the modes of linking one monosaccharide nucleus to another were established: and it was not until all had been made ready that a real attempt was made to discover the molecular groupings of inulin, cellulose, starch, and glycogen. The research has now entered this ultimate stage; and although at present it is too soon to speak of finality, nevertheless our knowledge of the polysaccharides has grown almost out of recognition within the last few years.

The remainder of this chapter is mainly concerned with the developments produced by the application of methylation in the carbohydrate group. While studying it, the reader may perhaps be inclined to suppose that it represents a record of easy and steady progress along well-defined lines; but it should be borne in mind throughout that in actual practice the carbohydrates present the most unexpected difficulties, both in experimental work and in the interpretation of results obtained. Consultation

<sup>1</sup> Denham and Woodhouse, *J.*, 1913, 103, 1735.

<sup>2</sup> Haworth, *J.*, 1915, 107, 8.

<sup>3</sup> Haworth and Leitch, *J.*, 1918, 113, 188; 1919, 115, 809; Haworth and Hirst, *J.*, 1921, 119, 193.



of the original papers will soon remove any false ideas on this subject which might be produced by the simplicity of text-book presentation.

### B.—THE PHENOMENA OF MUTAROTATION

When a monosaccharide such as glucose is dissolved in water, the optical rotatory power of the solution gradually alters until at last it reaches a constant value. The final stage can be reached more rapidly, either by heating the solution or by adding some catalyst such as ammonia. This change in the value of the rotatory power is known as mutarotation.

As an explanation of this behaviour, it was suggested<sup>1</sup> that mutarotating sugars exist in isomeric forms which, in solution, gradually change into one another. This explanation was later on supported by definite evidence. For example, when *d*-glucose is recrystallized from alcohol, it melts at 146° C. This form is termed  $\alpha$ -glucose. If a concentrated solution of  $\alpha$ -glucose be heated for several hours to 105°–106° C. and be then treated with alcohol, a fresh form,  $\beta$ -glucose,\* is obtained, which melts at 148°–150° C.†

These two modifications of glucose differ in solubility, the  $\beta$ -form being the more soluble. A more interesting difference comes to light when their rotatory powers are examined.<sup>2</sup> When 8 per cent. solutions are used, the initial rotatory power of the  $\alpha$ -modification is +110°, but, on standing, it gradually falls to +52°. The initial rotatory power of the  $\beta$ -modification is

<sup>1</sup> Erdmann, *Jahresbericht*, 1855, 672; 1856, 639; Dubrunfaut, *Compt. rend.*, 1856, 42, 739; Bechamp, *ibid.*, 896.

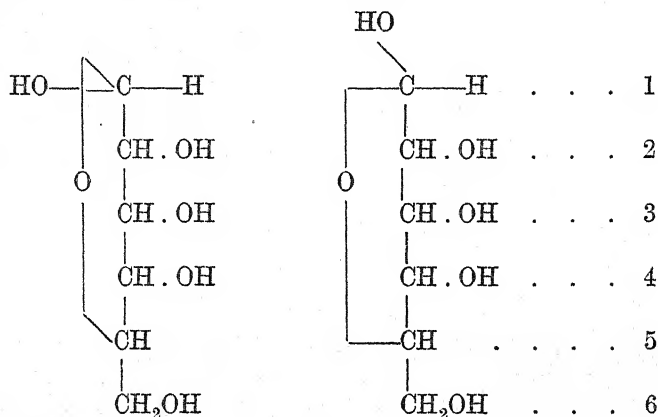
\* This substance was originally termed  $\gamma$ -glucose, as the name  $\beta$ -glucose had been given to an equilibrium mixture of  $\alpha$ - and  $\beta$ -glucose. On the discovery that this mixture was not an individual, the name  $\beta$ -glucose was transferred to the pure second variety. The term  $\gamma$ -glucose now denotes a peculiar active form of glucose, different from both  $\alpha$ - and  $\beta$ -forms.

† Hudson and Dale (*J. Amer. Chem. Soc.*, 1917, 39, 320) have shown that either of the two forms of glucose can be conveniently obtained by using acetic acid as a crystallizing medium.  $\alpha$ -Glucose is prepared by evaporating at ordinary temperature a mixture of two parts sugar, one part water, and four parts of glacial acetic acid.  $\beta$ -Glucose is obtained from a mixture of ten parts of sugar, one part of water, and twelve parts of glacial acetic acid by heating the solution on a boiling water-bath and subsequently allowing crystals to form.

<sup>2</sup> References to the literature of mutarotation are to be found in a paper by Hudson (*J. Amer. Chem. Soc.*, 1910, 32, 889). See also Baker, Ingold, and Thorpe, *J.*, 1924, 125, 268; Lowry, *J.*, 1925, 127, 1371; Lowry and Richards, *ibid.*, 1385.

- + 19°, but it slowly increases, on standing, to + 52°. This value, + 52°, obviously represents the rotation of a mixture of the two forms after they have come into equilibrium with each other.

To account for mutarotation, Tollens<sup>1</sup> suggested that sugar structures contain an oxide ring, which would bring into existence two fresh stereoisomeric forms of the sugar. The formulæ below represent the spatial arrangements round the terminal atom of the sugar chain in the two cases.



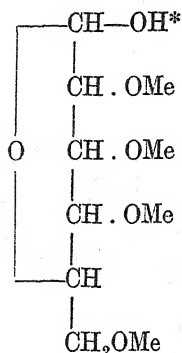
Support was lent to this hypothesis by the discovery that the alkyl glucosides occur in two stereoisomeric forms, which can be represented by replacing the hydroxyl groups attached to the carbon atoms (1) in the above formulæ by methoxyl radicles. A further proof of the correctness of Tollens' views is found in the behaviour of the methylated sugars and their glucosides. Tetramethyl-glucose exhibits mutarotation, whereas the corresponding tetramethyl-derivatives of the methylglucosides are devoid of mutarotatory power.<sup>2</sup>

As can be seen from these formulæ, the methylglucoside has no power of structural alteration, since it is completely methylated; whereas in tetramethyl-glucose the hydrogen atom marked with the asterisk might be assumed to wander and thus produce a new oxide-ring having a stereochemical position different from the original one.

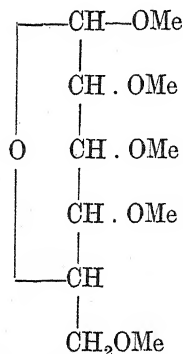
<sup>1</sup> Tollens, *Ber.*, 1883, 16, 923.

<sup>2</sup> Purdie and Irvine, *J.*, 1904, 85, 1049.





Tetramethyl-glucose.



Tetramethyl-methylglucoside.

If still further proof is needed in favour of the presence of an oxide-ring, it is to be found in the results of methylation; but as these will be discussed in detail in later sections of this chapter, it is unnecessary to go into the matter at this point.

The existence of an oxide-ring of some sort in the sugar structures is now generally admitted. But this by no means disposes of the problem, since the question at once presents itself: what is the nature of the ring? Since glucose, for example, contains five hydroxyl groups, each of which—theoretically—might play its part in the formation of an oxide-ring, it is evident that further evidence will be required in order to assign a definite ring-structure to the substance.

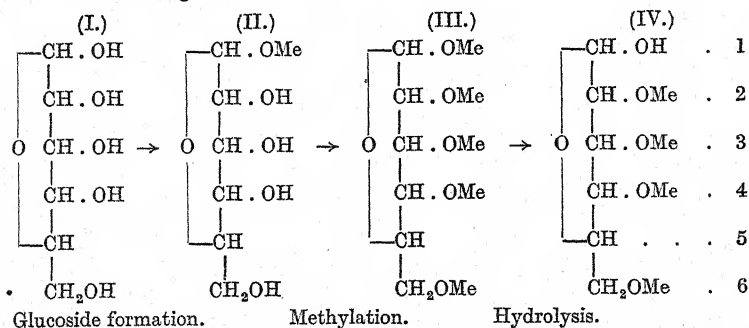
Very brief consideration will show how difficult is the problem thus presented to the chemist. In the first place, the ease with which mutarotation occurs, and the readiness with which the sugars react in the open-chain aldehydic form with phenylhydrazine and other similar reagents, are sufficient to prove that the oxide-ring is anything but a stable grouping. Under the action of even the mildest reagents a structural or stereochemical rearrangement may occur which may change the number of atoms in the ring or alter the spatial configuration of the molecule. Thus, even among the monosaccharides, it is difficult to gain absolute certainty as to the cyclic grouping, and in the polysaccharides this difficulty is increased. During the action of hydrolytic agents, the original ring-structure may be ruptured and a fresh type of ring may present itself in the constitution of the fission-products, so that a study of

their architecture might lead to completely erroneous inferences with regard to the type of ring present in the parent molecule.

In order to avoid this pitfall, it is obviously essential to put out of action all the hydroxyl groups in the carbohydrate molecule which might serve as centres for the formation of an oxide-ring different from that which is normally present. Various methods might be suggested, such as acetylation or benzoilation; but the drawbacks of such solutions of the problem are self-evident in the case of the polysaccharides. In this group, information can be gained only by splitting up the molecule by hydrolysis; and in the presence of hydrolytic agents there would be no guarantee that acetyl or benzoyl groups would remain *in situ*.\* What is required, evidently, is some substituent which will resist hydrolysis and will not migrate during hydrolytic reactions. Since this desideratum has been discovered in the methyl radicle, the methylation of the hydroxyl groups has become a process of fundamental importance in the study of carbohydrate constitution.

### C.—THE ALKYLATION OF THE CARBOHYDRATES

Before describing the practical methods employed in the alkylation of the carbohydrates, a typical example may be chosen in order to show the rationale of the processes employed; and for this purpose the stages leading up to the complete methylation of glucose may be selected. These are indicated in the following scheme<sup>1</sup> :—



\* For examples of the migration of acetyl groups in the acetylated rhamnoses, see Fischer, Bergmann, and Rabe, *Ber.*, 1920, 53, 2362. Compare also the kindred phenomena in the depside series which are described in Chapter XI.

<sup>1</sup> Irvine, *J.*, 1923, 123, 988.

The first stage is the formation of the methylglucoside in which the reducing group of the sugar is protected by the new methyl radicle. In the next stage, the methylating agent attacks the remaining hydroxyl groups of the molecule, the process culminating in the formation of the tetramethyl-methylglucoside (III.). When this is subjected to acid hydrolysis, the only methyl group removed is that related to the original reducing group of the sugar, so that the tetramethyl-derivative (IV.) is produced. This substance, as the formula shows, has four hydroxyl groups (in the 2 : 3 : 4 : 6-positions) masked by the alkyl radicles, and it is thus possible to study the properties of the reducing group in position 1 in the absence of many factors which might normally complicate the problem.

Further consideration will show that if a sugar derivative contains any group or groups capable of subsequent removal by hydrolysis, it is possible to methylate the unoccupied hydroxyl radicles and ultimately to obtain identifiable partly-methylated sugars. Thus the method of alkylation leads ultimately to an exact knowledge of the constitution of the compound subjected to methylation; but in order to make the identification it is essential to have a whole series of known reference-compounds in the form of more or less completely alkylated simple sugars. The preparation and identification of these substances occupied one of the longest and most laborious sections of the new attack on the carbohydrate constitutions.

We must now turn to the practical methods which have been devised in order to introduce alkyl groups into the carbohydrate molecules.

The pioneers in this branch of the subject were Purdie and Irvine,<sup>1</sup> who showed that sugars and glucosides would be alkylated by acting on them with alkyl iodides and dry silver oxide, a process generally termed for convenience "the silver oxide method." Since silver oxide has an oxidizing action on the reducing group of some sugars, it is usual to prepare the methylglucoside and utilize it for methylation, instead of the sugar itself.\* In this case, methylation is initially conducted

<sup>1</sup> Purdie and Irvine, *J.*, 1903, 83, 1021; 1904, 85, 1049; Irvine and Cameron, *ibid.*, 1071.

\* The methylglucosides, being more soluble in organic media than the parent sugars, are on this account better fitted for use in the silver oxide method of alkylation.

- in methyl alcohol solution. When several alkyl groups have been introduced into the sugar, the new derivative is soluble in methyl iodide, and thus the presence of methyl alcohol is no longer necessary.

The silver oxide method has the disadvantages that it is applicable only to carbohydrates for which a suitable solvent can be found; also that there is always a risk of the sugar being oxidized by the silver oxide; and finally, that the reagents are expensive. On the other hand, owing to the mild conditions under which methylation proceeds, no profound alterations in the constitution of the sugars need be feared when this method is employed. Racemizations, Walden inversions, or glucosidal interconversions do not complicate the problem. Thus the silver oxide method has furnished a safe means of preparing a large number of standard alkylated sugars which serve as comparison materials when other methylation methods, more violent in action, are employed.

- A fresh reagent for the methylation of the carbohydrates was discovered ten years later by Denham and Woodhouse.<sup>1</sup> They were engaged in an attempt to methylate cellulose; and since the insolubility of this material in normal solvents stood in the way of an application of the silver-oxide method, they tried the effect of methyl sulphate. By impregnating cellulose with a 15 per cent. solution of sodium hydroxide and then treating the material with methyl sulphate, they readily obtained methyl-derivatives of cellulose.

Two years later, Haworth<sup>2</sup> showed that methyl sulphate could be utilized very simply for the alkylation of less complex carbohydrates. The sugar, such as sucrose, was dissolved in a minimum quantity of water and the solution was introduced into a flask furnished with a condenser and two tap-funnels which contained respectively methyl sulphate and a 30 per cent. sodium hydroxide solution. The flask was placed on a water-bath maintained at 30°–40° C. and the reagents were run in from the tap-funnels with constant stirring, the temperature being raised to 70° C. in the later stages. The methylated sugar is extracted by means of chloroform, after any excess methyl sulphate has been destroyed; and the final purification is

<sup>1</sup> Denham and Woodhouse, *J.*, 1913, 103, 1735.

<sup>2</sup> Haworth, *J.*, 1915, 107, 8.



attained by vacuum distillation at low pressure. Haworth's method has the advantage that it proceeds in definite stages; so that homogeneous products, representing the intermediate steps in the alkylation process, can be isolated. Thus the production of mixtures of unchanged and partly-alkylated materials, which are found in using the silver oxide method, is avoided; and consequently the final purification of the end-product is simpler.

Yet another method of alkylation has been rendered possible by Werner's discovery that diazomethane can be easily obtained from nitroso-methylurea; and that alkylation by means of this reagent can be carried out in alcoholic solution.<sup>1</sup> The substance to be alkylated is dissolved in dry alcohol along with a small excess of nitroso-methylurea. Sodium ethoxide is added; and the diazomethane, thus liberated, immediately attacks the hydroxyl groups. Diazomethane is especially suitable for the methylation of phenolic groups in certain glucosides.<sup>2</sup>

#### D.—THE OXIDE-RINGS IN THE SUGARS

##### 1. General

As was mentioned in a previous section, the existence of an oxide-ring in the sugar molecule was suggested in order to account for the phenomena of mutarotation. At a later stage, Fischer's preparation of two isomeric methylglucosides and the isolation of glucose itself in isomeric forms furnished further support to the idea. Another branch of the evidence came to light when Purdie and Irvine<sup>3</sup> showed that the methylation of either methylglucoside yielded two isomeric tetramethylglucosides which on hydrolysis gave the same tetramethylglucose; and that from this tetramethylglucose the two original tetramethylglucosides could be obtained by ordinary glucoside formation. Though the evidence in favour of a ring-structure is by no means conclusive, it has been sufficient to satisfy most experts; and since in cyclic anhydrides and lactones a five-membered grouping is found to be the most stable type, the oxide-ring of the sugars was tacitly assumed to contain four carbon atoms and one oxygen atom.

<sup>1</sup> E. A. Werner, *J.*, 1919, 115, 1093.

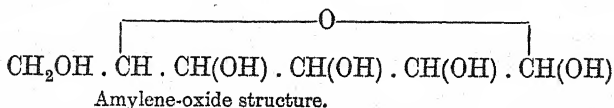
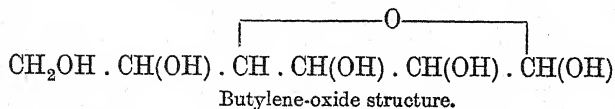
<sup>2</sup> Herzig and Schönbach, *Monatsh.*, 1912, 33, 673.

<sup>3</sup> Purdie and Irvine, *J.*, 1904, 85, 1059.



In his original work on the methylglucosides, Fischer<sup>1</sup> obtained three products. Two of these he regarded as stereoisomeric compounds, giving them the names of  $\alpha$ - and  $\beta$ -methylglucosides. The third substance, being difficult to purify, was not closely investigated; but Fischer assumed that it was glucose dimethyl-acetal. In 1914, however, Nef<sup>2</sup> put forward the view that the two methylglucosides were structural isomers and not stereoisomeric compounds; and thus the problem of the nature of the oxide-ring was raised in an acute form, since if the glucosides were structural isomers the oxide-rings in the two compounds must be different from each other.

Fischer<sup>3</sup> in his reply was able to show that the  $\alpha$ - and  $\beta$ -glucosides were structurally identical; but being thus led to a re-examination of the supposed glucose dimethyl-acetal, he was forced to conclude that it also was a methylglucoside, to which he gave the name  $\gamma$ -methylglucoside.\* This discovery of Fischer's was sufficient to establish that more than one kind of oxide-ring was possible in the sugar group; for the difference between the  $\gamma$ -glucoside and the other two must be a structural one, since the two stereochemical possibilities have already been utilized to account for the existence of the  $\alpha$ - and  $\beta$ -glucosides. But if two types of ring were possible, there was no guarantee that the normal type was a five-membered structure; and so the whole problem had to be approached from a fresh direction. In the group of aldoses, the two most probable structures appeared to be the five-membered butylene-oxide type and the six-membered amylenoxide structure:



<sup>1</sup> Fischer, *Ber.*, 1893, 26, 2405; 1895, 28, 1151, 1434.

<sup>2</sup> Nef, *Annalen*, 1914, 403, 204.

<sup>3</sup> Fischer, *Ber.*, 1914, 47, 1980.

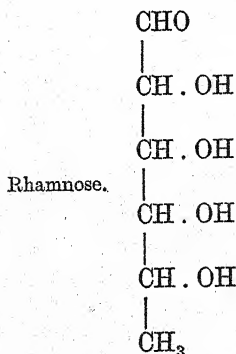
\* It should be noted that Fischer used the prefix  $\gamma$ - as a mere convenient symbol and that he did not mean to imply that the prefix had the same significance which it bears in, for instance,  $\gamma$ -lactone.

and it was at this point that the investigators reaped some of the fruits of the laborious work undertaken in the original preparation of the methylated sugars.

In dealing with sensitive materials like the carbohydrates, the possibility of isomeric change cannot be left out of account in considering the results of oxidation reactions; and the advantage of methylated sugars over other derivatives is to be found in the fact that the former can be oxidized without any change occurring in the relative positions of the various alkyl groups.<sup>1</sup> Thus the final products give a definite clue to the original grouping of the molecule.

## 2. Rhamnose

In order to make the method clear, the case of rhamnose<sup>2</sup> will be chosen, since it is free from complexities which arise in some other cases owing to mixtures being formed on methylation. When methylated by several different methods, rhamnose is invariably found to give on hydrolysis a single trimethyl-derivative. A glance at the rhamnose formula (written in the open-chain way to avoid any prejudice about the position of the ring) will show that a number of choices can be made for the positions of the three methoxy-groups:

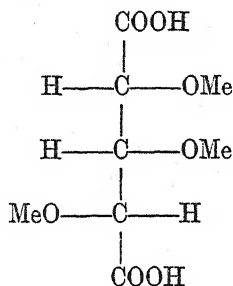


<sup>1</sup> Irvine, Fyfe, and Hogg, *J.*, 1915, 107, 539; Irvine and Oldham, *J.*, 1921, 119, 1744; Pryde, *J.*, 1923, 123, 1808; Haworth and Baker, *J.*, 1925, 127, 365; Levene, *J. Biol. Chem.*, 1924, 60, 167.

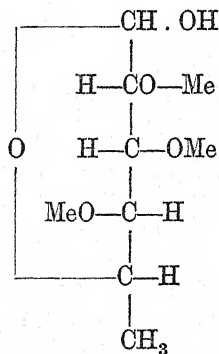
<sup>2</sup> Hirst and Macbeth, *J.*, 1926, 129, 22.

- The hydroxyl group which is unattacked by methylation is obviously the one which has lost its hydrogen atom in order to form the cyclic chain of the oxide-ring; and thus, if the positions of the three methoxy-radicles can be ascertained, the point of attachment of the oxide-ring is also established.

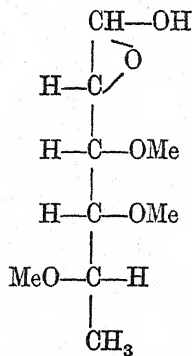
Now on oxidation with nitric acid, trimethyl-rhamnose yields *l*-arabo-trimethoxy-glutaric acid, the space formula of which is:



This result proves beyond doubt that the three methoxy-groups in trimethyl-rhamnose lie on three directly-connected carbon atoms. But this limits the possible formulæ of trimethyl-rhamnose to the two which are shown below:

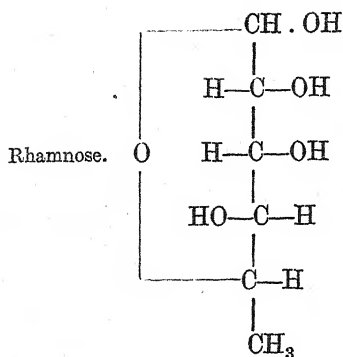


Trimethyl-rhamnose.



Alternative formula.

The choice thus lies between an ethylene-oxide ring and an amylen-oxide grouping; and on stereochemical and other grounds the amylen-oxide arrangement appears to be the only probable one. The formula of rhamnose itself must therefore be that shown below.



This example brings out clearly the value of sugar-methylation in problems of this type. In a similar manner it was proved that the pentoses xylose and arabinose also contain the amylene-oxide structure.<sup>1</sup>

### 3. The Glucoses

At first sight, the structure of glucose appears to present a problem of much greater difficulty than that of the rhamnose constitution. In 1925, an amylene-oxide ring structure for the glucose molecule was suggested<sup>2</sup>; and evidence in favour of this view<sup>3</sup> was found in the work of Hudson. This investigator<sup>4</sup> had shown, from an examination of two dozen lactones derived from the polyhydroxy-acids of the sugars, that a striking parallelism could be traced between the sign of rotation of the lactone and the position of the lactone ring assuming that ring-formation took place through the  $\gamma$ -carbon atom of the chain. No exceptions to the Hudson Rule have yet been detected. On the other hand, if the lactone ring were formed through the  $\alpha$ -,  $\beta$ -, or  $\delta$ -atom of the sugar chain, Hudson's Rule should fail in 8, 10, and 12 cases respectively out of the twenty-four. By applying the Hudson Rule to the case of the lactone derived

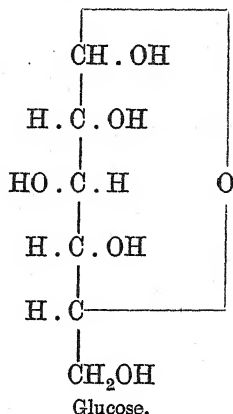
<sup>1</sup> Hirst and Purves, *J.*, 1923, 123, 1352; Hirst and Robertson, *J.*, 1925, 127, 358.

<sup>2</sup> Haworth, *Nature*, 1925, 116, 430.

<sup>3</sup> Charlton, Haworth, and Peat, *J.*, 1926, 129, 89.

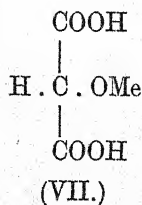
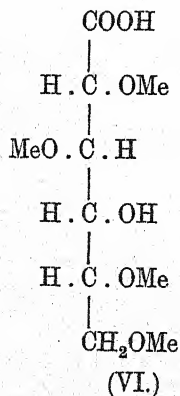
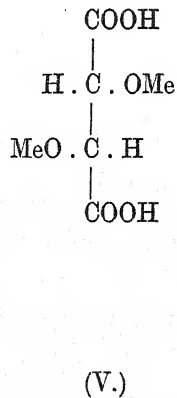
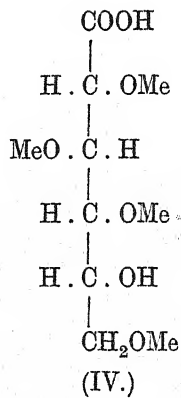
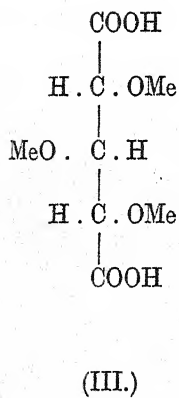
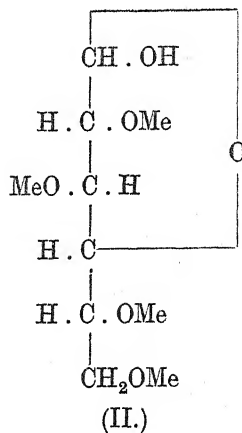
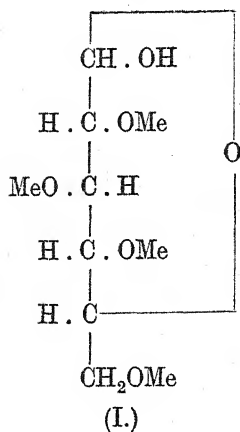
<sup>4</sup> Hudson, *J. Amer. Chem. Soc.*, 1910, 32, 338.

from tetramethyl-glucose, Charlton, Haworth, and Peat came to the conclusion that glucose must contain the amylenoxide ring; so that the glucose molecule should have the structure:

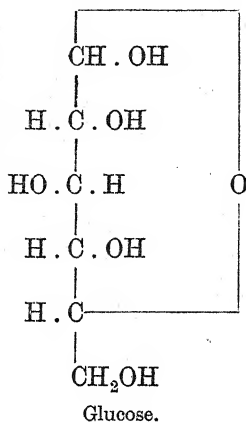


Strong evidence in favour of the amylenoxide structure has been contributed by the study of the oxidation-products of tetramethyl-glucose. On methylation, glucose yields a tetramethyl derivative. If an amylenoxide ring exists in the glucose structure, then this tetramethyl derivative must be the 2:3:4:6 compound shown in formula (I.); whereas if a butyleneoxide ring is present, the tetramethyl-derivative will be the 2:3:5:6 compound shown in (II.). See p. 52.

If the amylenoxide ring be present in the molecule, the first result of oxidation would be the production of the tetramethyl-gluconic acid (IV.). Thereafter, *d*-dimethoxy-succinic acid (V.) would be formed if the break took place between the fourth and fifth atoms of the chain, or else the product would be inactive xylo-trimethoxy-glutaric acid (III.), if rupture occurred between the fifth and sixth atoms of the chain. If the butyleneoxide ring be present, on the other hand, the first product would be the tetramethyl-gluconic acid shown in (VI.). On further oxidation, this might yield methoxy-malonic acid (VII.) and also the same dimethoxy-succinic acid (V.) as would be obtained from the amylenoxide structure. From this it is evident that the presence or absence of the xylo-trimethoxy-glutaric acid (III.) is the crucial test in deciding between the two possible ring-structures.



This field has been investigated by Hirst,<sup>1</sup> who detected xylo-trimethoxy-glutaric acid among the oxidation products; and by means of the reasoning already given, he was able to establish definitely that the true formula of glucose is :



The foregoing examples will suffice to illustrate the methods by which the presence of the amylenoxide ring has been established in the cases of certain normal sugars. It will be remembered, however, that the existence of a third methylglucoside suggests the probability that more than one type of ring-structure is possible in the sugar molecule; and this idea gains further support from the readiness with which sucrose and other fructosides are hydrolysed, for their lability suggests that they are constituted differently from the normal type.

Irvine, Fyfe, and Hogg, simultaneously, with Fischer,<sup>2</sup> discovered the existence of the third methylglucoside, which they isolated in the course of an attempt to prepare glucosamine from glucose; and their investigations of it carried our knowledge considerably further. Fischer<sup>3</sup> observed that the  $\gamma$ -methylglucoside differed from the  $\alpha$ - and  $\beta$ -forms in its indifference to emulsin, as well as in its extraordinary sensitiveness towards acids. Irvine, Fyfe, and Hogg found that in addition to these properties, the  $\gamma$ -glucoside is characterised by (1) the remarkable

<sup>1</sup> Hirst, *J.*, 1926, 129, 350.

<sup>2</sup> Irvine, Fyfe, and Hogg, *J.*, 1915, 107, 524.

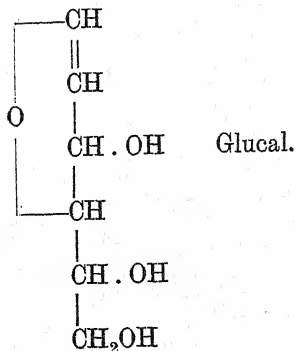
<sup>3</sup> Fischer, *Ber.*, 1914, 47, 1980.



ease with which it enters into condensation with acetone ; (2) its capacity of reducing alkaline potassium permanganate, which is so striking as to suggest unsaturation ; (3) its tendency to unite with one atomic proportion of oxygen to give a neutral product ; and (4) the ready auto-condensation of this oxy-compound to give a product allied to the disaccharides. These properties were practically unique in the sugar group.

Irvine, Fyfe, and Hogg, on methylating this  $\gamma$ -methylglucoside by means of silver oxide, obtained a tetramethyl- $\gamma$ -methylglucoside which was found to differ completely in properties from the methylation-products of the  $\alpha$ - and  $\beta$ -methylglucosides. It reduced permanganate instantaneously in the cold and was readily hydrolysed by hydrochloric acid in conditions which leave the  $\alpha$ - and  $\beta$ -forms intact. The hydrolysis product is a tetramethylated hexose, termed tetramethyl- $\gamma$ -glucose, which is a liquid, instead of being solid like the normal tetramethyl-glucose obtained from either the  $\alpha$ - or the  $\beta$ -methylglucoside.

The reaction with permanganate suggests the possibility that the  $\gamma$ -methylglucoside contains an unsaturated linking and might therefore be allied to glucal, for which Fischer<sup>1</sup> had proposed the following formula :

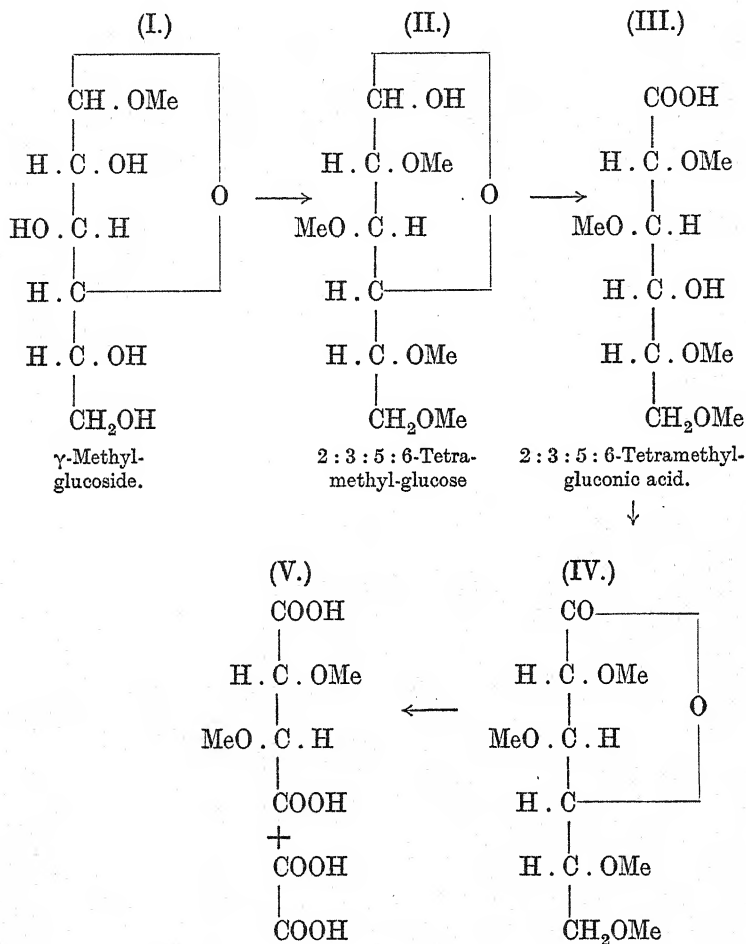


The most convincing evidence on the point is the following.<sup>2</sup> When  $\gamma$ -methylglucoside (I.) is methylated and then hydrolysed, it yields 2 : 3 : 5 : 6-tetramethyl-glucose (II.). Oxidation of this

<sup>1</sup> Fischer, *Ber.*, 1914, 47, 196.

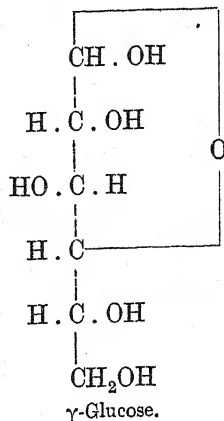
<sup>2</sup> Haworth, Hirst, and Miller, *J.*, 1927, 2436 ; Haworth, *Constitution of Sugars* (1929), p. 42.

with bromine water gives 2:3:5:6-tetramethyl-gluconic acid (III.). The lactone of this (IV.), when digested with hot nitric acid, is oxidised to oxalic acid and *d*-dimethyl-tartaric acid (V.).



As there is no doubt about the structure<sup>1</sup> of the lactone (IV.) it is easy to work backwards to the structure of  $\gamma$ -glucose itself, which can be inferred from that of the  $\gamma$ -methylglucoside (I.). On this evidence,  $\gamma$ -glucose must have the structure shown below.

<sup>1</sup> Haworth, *Constitution of Sugars* (1929), p. 19.



#### 4. The Fructoses

Since fructose is associated with glucose in the sucrose molecule, it seemed advisable to determine whether fructose also was capable of existing in a labile form, as this would open the way to the investigation of the sucrose structure. The results obtained in this field by Irvine and Robertson<sup>1</sup> were of unexpected complexity. Clear evidence was obtained that fructose reacts in two forms. (1) A compound containing a normal oxide-ring and existing in two modifications termed the  $\alpha$ - and  $\beta$ -forms. On methylation each of these gives rise to a tetramethyl-fructoside which may be hydrolysed to a tetramethyl-fructose. These, like the parent sugar, are lævo-rotatory and may be supposed to have the same type of oxide-ring. This fructose type is not attacked by permanganate, should not combine readily with acetone, and should give rise to stable fructosides. It is represented by the ordinary crystalline form of fructose. (2) A more reactive compound, now known as  $\gamma$ -fructose. This variety of fructose is highly reactive, combines readily with acetone, and reduces permanganate solution. Fructosides derived from this type of fructose are hydrolysed by acids in low concentrations.

The views of Irvine and Robertson received strong support from other facts discovered at a later stage.<sup>2</sup> It is well known to every chemist that when dextro-rotatory cane-sugar (sucrose) is hydrolysed with dilute acids, the resulting mixture of glucose

<sup>1</sup> Irvine and Robertson, *J.*, 1916, 109, 1305.

<sup>2</sup> Haworth and Law, *J.*, 1916, 109, 1314.

- and fructose is lævo-rotatory, whence is derived the term "inversion" to describe the process. The origin of the change in rotatory power is found in the fact that the dextro-rotatory sucrose molecule is split up into a dextro-rotatory glucose molecule and a lævo-rotatory fructose molecule of much higher rotatory power. The result of this is that the mixture possesses lævo-rotation. Now when sucrose is methylated and hydrolysed, the octamethyl-sucrose splits up into tetramethyl-glucose and tetramethyl-fructose; but *no inversion of the sign of the rotatory power is observed*. This apparent anomaly is due to the fact that the methylated fructose residue differs from ordinary fructose in being strongly dextro-rotatory instead of showing lævo-rotation. This furnishes conclusive proof that the fructose molecule is capable of existing in two different forms. As combined in the sucrose molecule, it is in the  $\gamma$ -form; and during the inversion of sugar it reverts to the normal stable fructose type. If this intramolecular rearrangement is prevented by methylation, which locks the molecular structure, then the
- product of inversion is the tetramethyl-derivative of the  $\gamma$ -form and not a derivative of the normal form. This conception of the matter is reinforced by the fact that tetramethyl-fructose<sup>1</sup> derived from the methylation of methyl-fructoside differs greatly in physical and chemical character from the tetramethyl-fructose obtained from octamethyl-sucrose. The former compound is stable towards permanganate, the sucrose product is unstable in presence of permanganate; and the two substances present the contrast in rotatory power which was referred to above.

Fructose, then, exists in two structurally different forms. With regard to the normal variety, the following evidence throws light on the constitution.

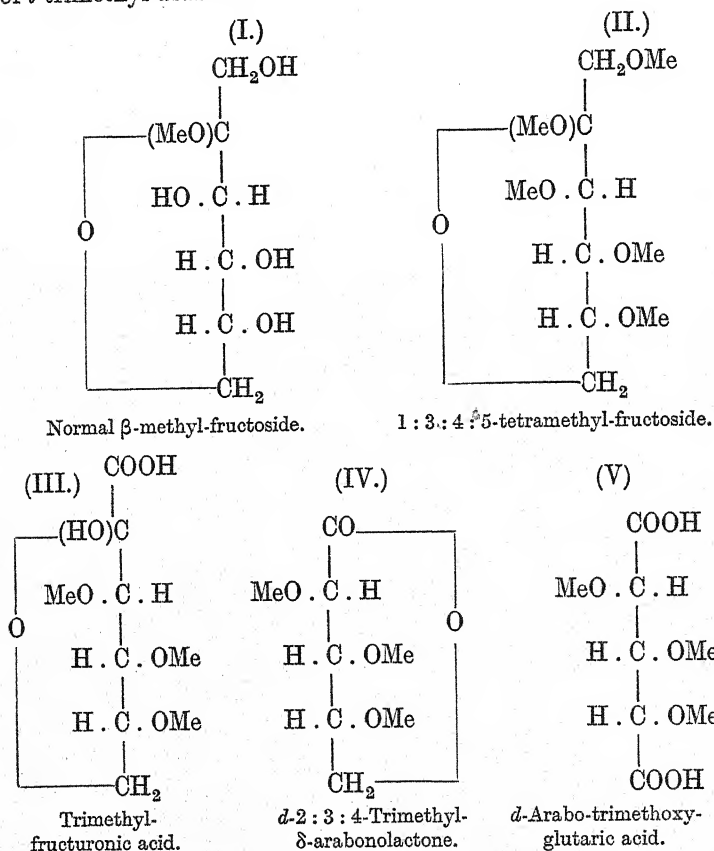
Fructose yields two methyl-fructosides, which are designated as  $\alpha$ - and  $\beta$ -methyl-fructoside.<sup>2</sup> Methylation<sup>3</sup> of  $\beta$ -methyl-fructoside (I.) yields 1:3:4:5-tetramethyl-fructoside (II.). Since there is no reducing group in the terminal position, this substance might be expected to be more stable than corresponding compounds derived from the aldoses; and in practice it is found that bromine water has very slight effect on the methylated

<sup>1</sup> Purdie and Paul, *J.*, 1907, 91, 296.

<sup>2</sup> Hudson, *J. Amer. Chem. Soc.*, 1916, 38, 1216.

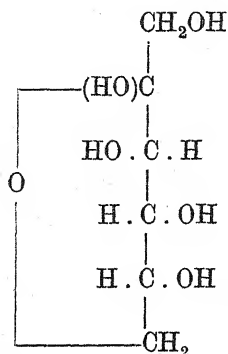
<sup>3</sup> Purdie and Paul, *J.*, 1907, 91, 289; Steele, *J.*, 1918, 257.

fructoside. Digestion with nitric acid,<sup>1</sup> however, leads to oxidation of the  $-\text{CH}_2\text{OMe}$  group, with the production of trimethyl-fructuronic acid (III.). (Arabo-trimethoxy-glutaric acid is formed as a by-product in this reaction.) When trimethyl-fructuronic acid is oxidized with acidified permanganate it yields *d*-2:3:4-trimethyl- $\delta$ -arabonolactone (IV.), which proves to be an optical enantiomorph of the product obtained by the action of bromine water upon *l*-trimethyl-arabinose. Further oxidation converts (III.) into *d*-arabo-trimethoxy-glutaric acid (V.), which is the optical antipode of the compound obtained by oxidation of *l*-trimethyl-arabinose.



<sup>1</sup> Haworth and Hirst, *J.*, 1926, 1858; Haworth, Hirst, and Learner, *J.*, 1927, 1040; Haworth, *Constitution of Sugars* (1929), p. 34.

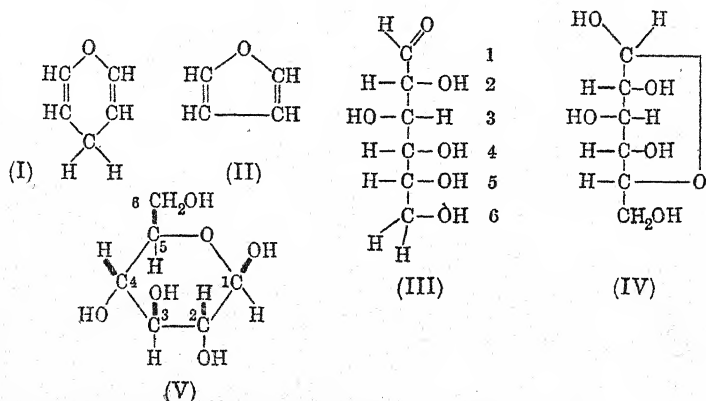
These results seem to leave no doubt that normal fructose has the following structure :—



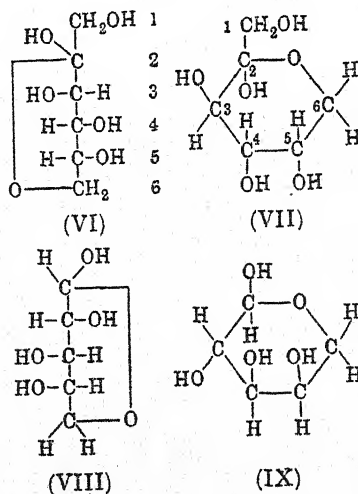
Normal fructose.

### 5. Sugars as Pyranoses and Furanoses

As normal hexoses and pentoses such as glucose, fructose and arabinose exist in the form of six-atom rings, and the labile or  $\gamma$ -sugars have a five-atom ring structure, they are regarded as being derivatives of pyran (I.) and furan (II.) respectively. It has consequently been proposed that such sugars should be named pyranoses and furanoses, and their formulæ brought into line with those representing pyran, furan and their other derivatives. Thus the formula (IV.) of  $\beta$ -glucose becomes structure (V.)



In structure (V.) the heavy lines indicate that the attached group or atom is above the plane of the ring. When the reader builds up this ring structure with model atoms from the open chain aldehyde structure of glucose (III.), it will be noticed that in bringing about ring closure to form the pyranose (V.) the hydrogen atom attached to carbon atom 5 swings round to the position opposite to that shown in structures (III.) and (IV.), and the  $-\text{CH}_2\text{OH}$  group takes the place vacated by the hydrogen atom. This gives on one side of the pyranose ring the groups  $-\text{CH}_2\text{OH}$ ,  $-\text{H}$ ,  $-\text{OH}$ , and  $\text{H}$  attached to carbon atoms 5, 4, 3, and 2 respectively. The structure (V.) shown represents  $\beta$ -glucose. When the hydroxyl group and hydrogen atom attached to carbon atom 1 are reversed  $\alpha$ -glucose is represented. Dealing with other formulæ in the same way fructose (VI.) becomes (VII.), and arabinose (VIII.) becomes (IX.).

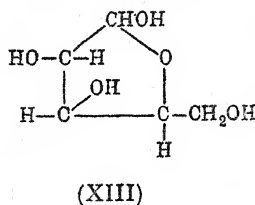
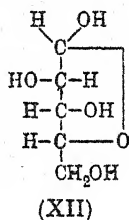
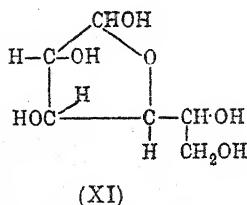
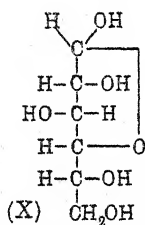


The derivatives of the  $\gamma$ -sugars fall into line as furans. Thus  $\gamma$ -glucose (X.) becomes (XI.), and  $\gamma$ -arabinose (XII.) becomes (XIII.)<sup>1</sup>

These ring formulæ have the advantage of making clearer many of the sugar reactions.

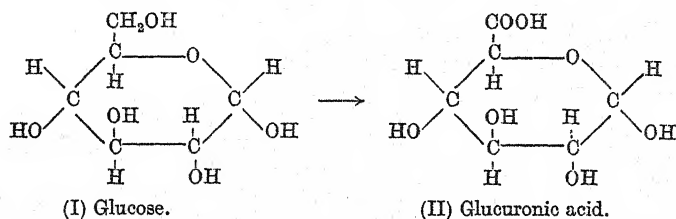
<sup>1</sup> Haworth, *The Constitution of Sugars*, 1929.





### 6. The Uronic Acids

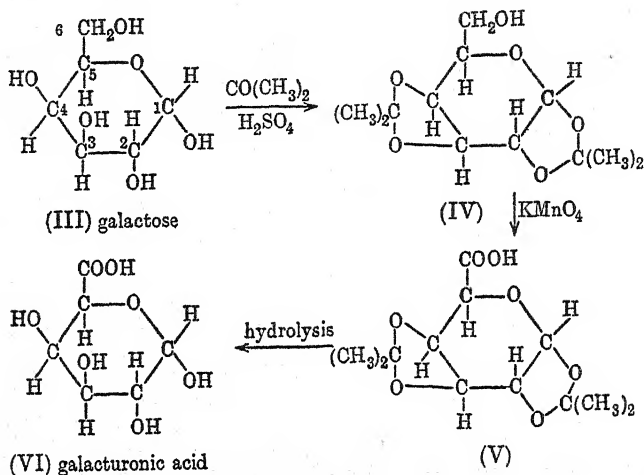
When the primary alcoholic group of a reducing monosaccharide such as glucose (I.) or galactose is oxidized to a carboxyl group, a uronic acid (II.) results.



The three dextro-acids derived from glucose, galactose, and mannose respectively are of interest as they occur in both the vegetable and animal kingdoms. *d*-Glucuronic acid has been isolated from gum arabic and the hemicelluloses, and occurs in combination in the glycoproteins; *d*-galacturonic acid is the chief constituent of pectin,\* and is present in polyuronides in a number of plant gums, mucilages and hemicelluloses; *d*-mannuronic acid,\* which readily reverts to the lactone, has been isolated from various marine algæ. *d*-Galacturonic acid has been synthesized from *d*-galactose (III.) in the following way. The diacetone-derivative, galactose diisopropylidene ether (IV.)

\* See Chapter IV.

was prepared by condensing the sugar with acetone in the presence of sulphuric acid. This derivative was oxidized with potassium permanganate to diisopropylidene-*d*-galacturonic acid (V.), which on hydrolysis with hot water yielded *d*-galacturonic acid (VI.).<sup>1</sup>



*d*-Mannuronic acid in the form of its lactone has been obtained from *d*-mannose by two different methods. In one method mannose was converted into  $\alpha$ -methylmannoside 2:3-mono-acetone. The primary alcoholic group was then oxidized by potassium permanganate to a carboxyl group. The acetone group was next split off by dilute hydrolysis to produce  $\alpha$ -methyl *d*-mannuronide. This glycoside was hydrolysed and the lactone of *d*-mannuronic acid isolated.<sup>2</sup> In the second method, which is an adaptation of the original procedure employed by Fischer and Piloty for the synthesis of *d*-glucuronic acid,<sup>3</sup> *d*-mannose (VII.) was converted into *d*-mannonic acid (VIII.) by electrolytic oxidation.\* This acid was further oxidized by nitric acid to *d*-mannosaccharic acid dilactone (X.). The dilactone was reduced by sodium amalgam in the presence of sulphuric acid.

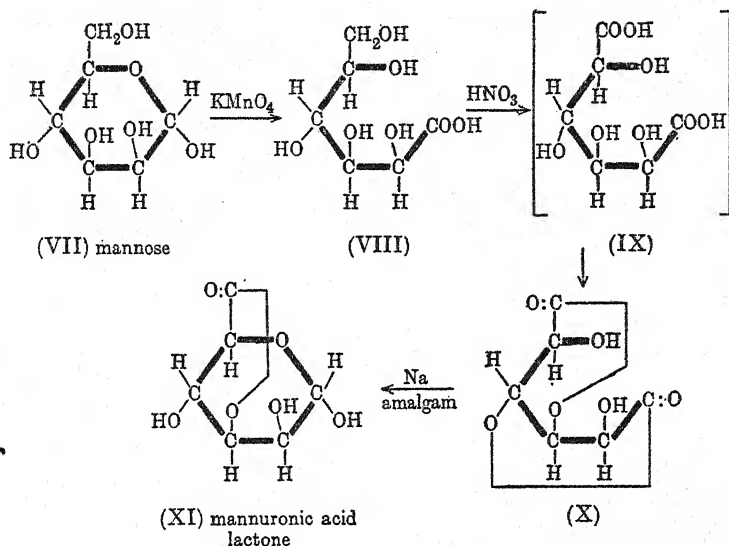
<sup>1</sup> Nieman and Link, *J. Biol. Chem.*, 1934, 104, 95, 743; 1934, 106, 773.

<sup>2</sup> Auld, Haworth, and Hirst, *J.*, 1935, 517.

<sup>3</sup> Fischer and Piloty, *Ber.*, 1891, 24, 521.

\* The process is carried out in the presence of calcium bromide, electrolytically formed bromine effecting the oxidation. Calcium carbonate is also present to produce crystalline calcium mannonate.

After purification *d*-mannuronic acid in the form of its barium salt was isolated. The salt was decomposed by acid and *d*-mannuronic acid lactone (XI.)<sup>1</sup> isolated. The structures are as follows :—



These syntheses of galacturonic and mannuronic acids from compounds of known configuration serve to establish their identities, and they, like their parent sugars, can exist in the  $\alpha$ - and  $\beta$ -forms.

## E.—THE DISACCHARIDES

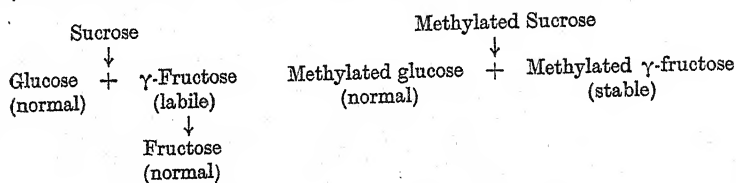
### 1. Sucrose

As most first-year students know, the hydrolysis of cane sugar yields a mixture of glucose and normal fructose; from which evidence it seems a simple matter to infer the constitution of the disaccharide. Further investigation, however, proved that matters were not quite so simple as they appeared.

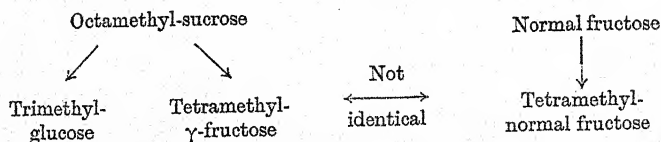
Methylation of sucrose produces octamethyl-sucrose; and when this is hydrolysed, it yields a mixture of methylated glucose and methylated fructose. The octamethyl-sucrose has a rotation

<sup>1</sup> Nieman and Link, *J. Biol. Chem.*, 1933, 100, 407.

$[\alpha]_D = +66.5^\circ$ , whilst the mixture after hydrolysis has  $[\alpha]_D = +56.5^\circ$ ; so that there is no change of sign as a consequence of the hydrolysis, and the case is not similar to the production of ordinary invert sugar from sucrose. To account for these phenomena, Haworth and Law<sup>1</sup> suggested that in the sucrose molecule, the fructose fragment exists in the  $\gamma$ -structure, but that when sucrose is hydrolysed, the liberated fructose reverts to the normal constitution. In the case of the methylated sucrose, however, the liberated fructose cannot change its structure owing to the presence of the methyl groups, and hence the substance produced by hydrolysis in this instance is a methylated  $\gamma$ -fructose and not a methyl derivative of normal fructose.



This idea received confirmation from further investigations by Haworth,<sup>2</sup> who isolated the pure methylated fructose fragment from the hydrolysis products of octamethyl-sucrose, and proved that it was a tetramethyl-fructose with properties different from those of the tetramethyl-derivative obtained from normal fructose.



Evidently, in order to establish the constitution of sucrose, it is essential to determine the structure of tetramethyl- $\gamma$ -fructose. This was achieved in the following manner.<sup>3</sup>

Sucrose was methylated and hydrolysed. The tetramethyl- $\gamma$ -fructose (I.) thus obtained was treated with nitric acid, whereby a terminal group was oxidised, with the loss of a methoxyl

<sup>1</sup> Haworth and Law, *J.*, 1916, 109, 1314.

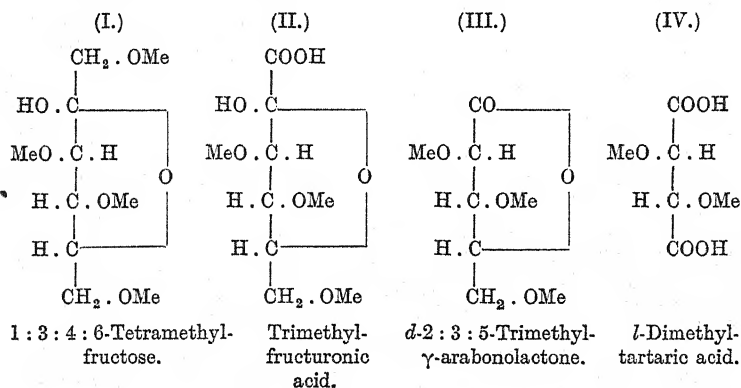
<sup>2</sup> Haworth, *J.*, 1920, 117, 199.

<sup>3</sup> Haworth, Hirst, and Nicholson, *J.*, 1927, 1513; Avory, Haworth, and Hirst, *ibid.*, 2308; Haworth, Hirst, and Learner, *ibid.*, 2432.

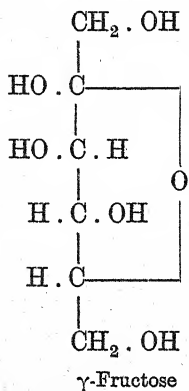
radicle. The resulting trimethyl-fructuronic acid (II.) reduced Fehling's solution; but when the reducing group was protected by methylation, the reducing power vanished.

When the trimethyl-fructuronic acid (II.) was treated with permanganate and dilute sulphuric acid, it yielded 2:3:5-trimethyl-*d*-arabonolactone (III.), which had a rotation equal in magnitude but opposite in sign to that of the *lævo*-variety, which had previously been isolated from *l*-trimethyl- $\gamma$ -arabinose. Further oxidation with nitric acid converted the lactone from sucrose into *l*-dimethyl-tartaric acid (IV.).

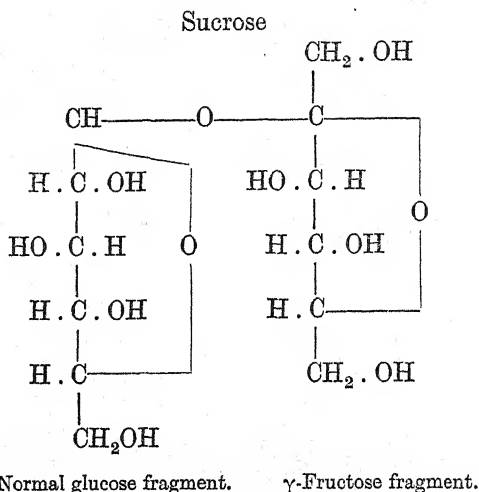
The only manner in which these results can be fitted together satisfactorily is shown in the following formulæ:—



This establishes the following constitution of  $\gamma$ -fructose:—



And now, since the glucose fragment of sucrose is a normal glucose, it is possible to link up the normal glucose and  $\gamma$ -fructose portions in the following manner, through the unmethylated group in the formula (I.) above, so as to form the complete sucrose molecule :—

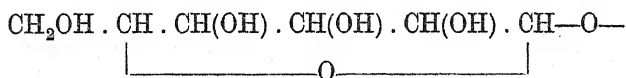


As has already been pointed out, when sucrose undergoes hydrolysis, the labile  $\gamma$ -fructose thus liberated is immediately transformed into the stable variety of fructose.

## 2. Maltose

When treated with dilute acids, the disaccharide maltose yields glucose exclusively as a hydrolysis product. It must, therefore, be built up from two glucose molecules; and the main point of interest lies in the determination of the manner in which the two monose molecules are united. But the importance of the maltose constitution ranges far beyond the structure of a single compound. The fact that diastase breaks down the starch molecule with the liberation of maltose is sufficient to indicate the prominence which the maltose structure attains in the chemistry of the higher carbohydrates.

For reasons which have already been given in connection with other sugars, it would be useless to attack the maltose problem through maltose itself, since during the hydrolytic degradation reactions there might be changes in the structures of the two glucose nuclei. As in other cases, methylation is the best available method of preventing such alterations, and this was first utilized by Purdie and Irvine<sup>1</sup> early in this century. Unfortunately, the action of silver oxide proved to be more complicated than had been hoped, since oxidation occurred at the reducing group of the sugar; yet one decisive result was attained. Crystalline tetramethyl-glucose was isolated from the reaction-products; and this revealed the structure of one-half of the maltose molecule to be the following, if the amylenoxide formula for glucose be adopted:



The non-reducing glucose residue of maltose.

A second attack on the problem was made later on by Irvine and Dick,<sup>2</sup> by means of complete methylation of methylmaltoside and an identification of the hydrolytic fission products; but it also met with unexpected obstacles, since the preparation of methylmaltoside, by the method employed, was found to involve the degradation of the sugar so that a methylated pentose appeared among the reaction-products.

A third attempt to solve the problem was made by Haworth and Leitch,<sup>3</sup> who applied the methyl-sulphate method to maltose in two stages, the first step being intended to convert maltose into methylmaltoside which was to be completely methylated in the second application of the reagent. The methylated methylmaltoside was then hydrolysed, and two methylated glucoses were identified in the products, one being tetramethyl-glucose. The new point of interest was reached when it was found that the second product was a trimethyl-glucose; and since this must be the key to the structure of the second half of the maltose molecule, its nature is of vital importance.

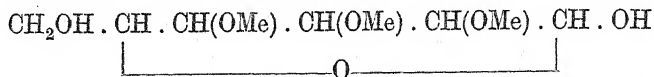
<sup>1</sup> Purdie and Irvine, *J.*, 1905, 87, 1022.

<sup>2</sup> Irvine and Dick, *J.*, 1919, 115, 593.

<sup>3</sup> Haworth and Leitch, *J.*, 1919, 115, 809.

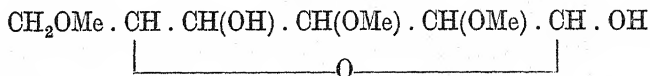


The sugar isolated by Haworth and Leitch was a syrup and was believed by them to be the liquid trimethyl-glucose in which the terminal  $\text{—CH}_2\text{OH}$  group is unsubstituted. Adopting the amylenoxide structure, such a substance has the formula



Implicit in this formulation is the conception that the two hexose nuclei in maltose are united through a terminal alcohol group; since only such groups are available for the purpose, owing to the remainder being blocked by methyl radicles.

The foregoing view of the trimethyl-glucose isolated from maltose could not, however, be reconciled with the results obtained in the methylation of starch and glycogen, which will be dealt with presently; and at a later date it was shown by Irvine and Black<sup>1</sup> (and independently by Cooper, Haworth, and Peat<sup>2</sup>) that this trimethyl-glucose is not 2:3:4-trimethyl-glucose (as had been assumed) but instead was 2:3:6-trimethyl-glucose:



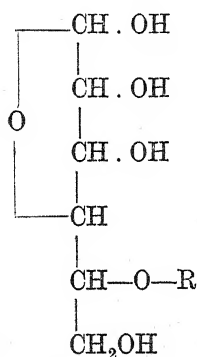
At first sight, this correction may appear to settle the problem of the maltose structure, since apparently we have now a knowledge of both halves of the maltose molecule. Confidence in this view must be shaken, however, when it is recalled that the number of diglucoses which can qualify for this mode of linkage is much greater than the stereochemical possibilities will permit. Thus the enigma of the maltose constitution apparently remains as insoluble as before.

Irvine and Black have pointed out a possible explanation of the phenomena. Suppose that two disaccharides had the

<sup>1</sup> Irvine and Black, *J.*, 1926, 129, 862.

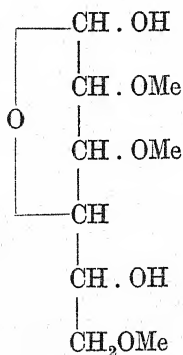
<sup>2</sup> Cooper, Haworth, and Peat, *J.*, 1926, 129, 876.

structures shown respectively in (A) and (B), in which R represents in each case the non-reducing hexose residue shown on p. 67. On methylation, the compound (B) would yield the stable form of 2:3:6-trimethyl glucose by direct reaction between the reagents. The compound (A), however, might yield the same derivative if an intramolecular change takes place subsequent to (or during) methylation and hydrolysis as shown in the formulæ :

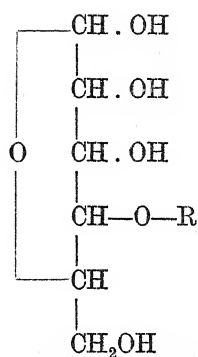


(A)

↓  
Methylation  
and hydrolysis.

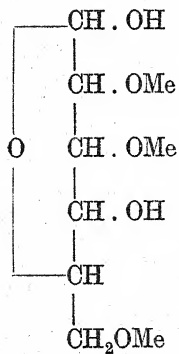


Unstable type.



(B)

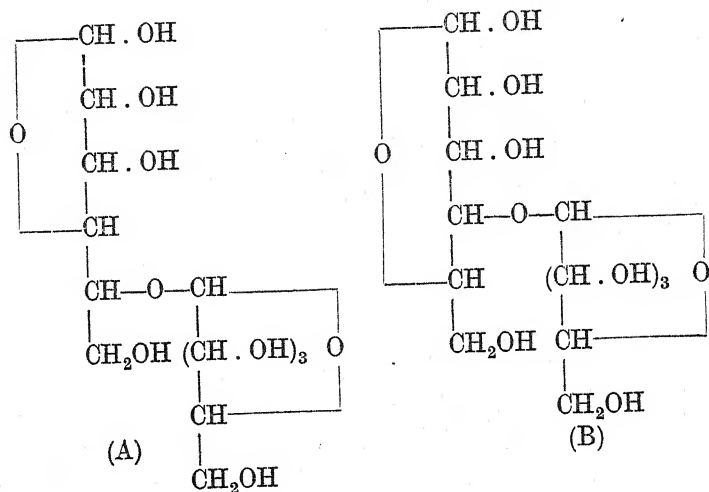
↓  
Methylation  
and hydrolysis.



Stable type.

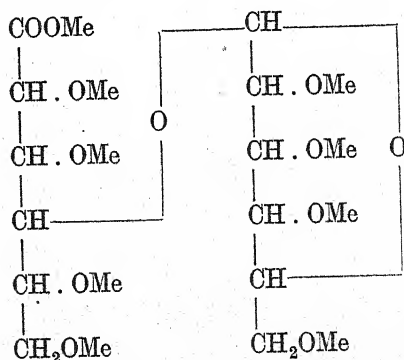
Intramolecular  
rearrangement.

This reasoning leaves open a choice between two possibilities in deciding upon a formula for maltose :



Alternative formulæ for maltose.

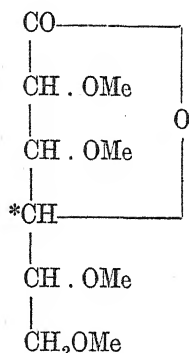
The choice between these alternatives can be made on the following evidence.<sup>1</sup> Maltose was oxidized to maltobionic acid. By methylating this last substance, octamethyl-maltobionate was obtained.



Octamethyl-maltobionate.

<sup>1</sup> Haworth and Peat, *J.*, 1926, 129, 3094.

On hydrolysis, this yields 2:3:5:6-tetramethyl- $\gamma$ -gluconolactone



from the left-hand section of the structure. This establishes the position of the linkage between the two sugar groups as being at the point marked with an asterisk, and this proves that the maltose formula (B) is correct.

### 3. Lactose

The constitution of lactose has been inferred by methods analogous to those which have just been described. On complete methylation,<sup>1</sup> lactose yields a heptamethyl-methylactoside, the cleavage products of which, after hydrolysis, are found to be 2:3:6-trimethyl-glucose and a tetramethyl-galactose. This last substance has been shown<sup>2</sup> to contain an amylene-oxide ring; so the lactose structural formula must be identical with one of the alternative formulæ for maltose which have just been given. The difference between the two sugars lies in the configurations of the non-reducing portion of the molecules. In maltose, this has the glucose configuration, whilst in lactose the non-reducing portion has the same configuration as the galactose molecule.

The constitution of the disaccharide cellobiose has been attacked in an analogous manner; but as its structure is intimately connected with the cellulose constitution, a discussion of its molecular arrangement will fall into place more appropriately at a later stage, in the section dealing with cellulose.\*

<sup>1</sup> Haworth and Leitch, *J.*, 1918, 118, 188.

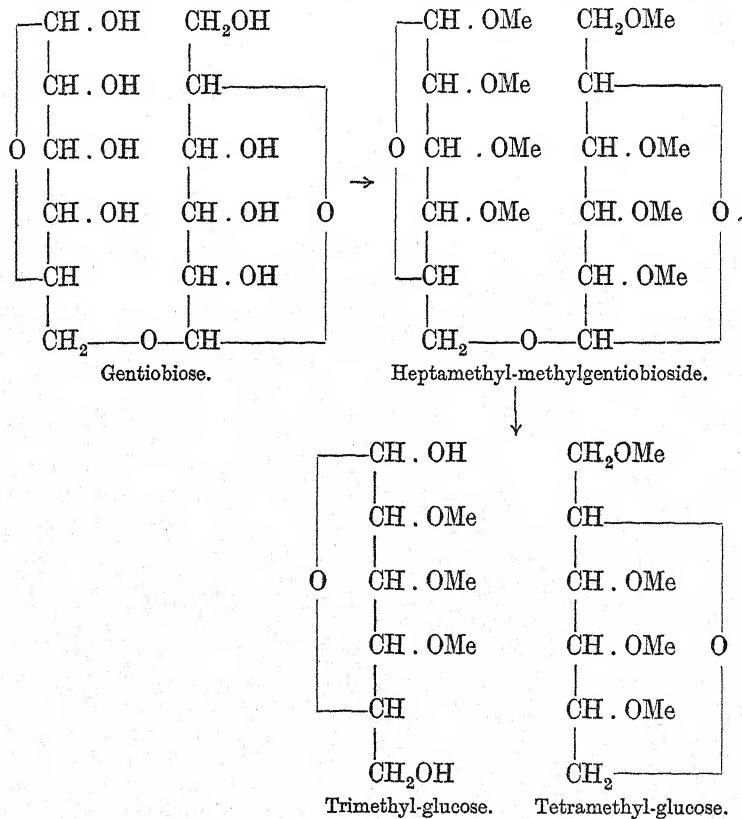
<sup>2</sup> Pryde, *J.*, 1923, 123, 1808; Haworth, Ruell, and Westgarth, *J.*, 1924, 125, 2468.

\* See p. 83.

## F.—GENTIANOSE

This substance is a trisaccharide,  $C_{18}H_{32}O_{16}$ , which is found in gentian roots. On partial hydrolysis with acids or by means of invertin, it can be decomposed into *d*-fructose and a disaccharide named gentiobiose. Gentiobiose can be synthesized from glucose by the action of emulsin,<sup>1</sup> but this merely proves that gentiobiose is built up from two glucose molecules and tells nothing with regard to which hydroxyl group of one sugar molecule is attacked by the aldehyde radicle of the second glucose molecule during the condensation.

Haworth and Wylam<sup>2</sup> have cleared up the matter in the

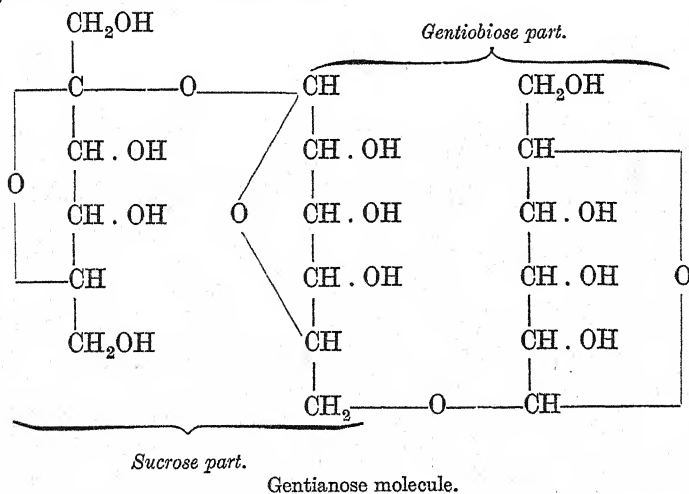


<sup>1</sup> Bourquelot, Hérissé, and Coirre, *Compt. rend.*, 1913, 157, 732; compare Georg and Pictet, *Helv. Chim. Acta*, 1926, 9, 444.

<sup>2</sup> Haworth and Wylam, *J.*, 1923, 123, 3120.

following manner. Gentiobiose was methylated by means of methyl sulphate followed by an application of the silver-oxide method; and in this way a heptamethyl-methylgentiobioside was obtained. On hydrolysis, this heptamethyl-derivative broke up into two methylated monoses which are now known to be 2:3:4-trimethyl-glucose and 2:3:4:6-tetramethyl-glucose. These facts indicate that the decomposition of gentiobiose can be expressed by the formulæ on p. 72.

Now the trisaccharide gentianose is built up from gentiobiose and fructose, since it can be decomposed into these constituents on hydrolysis; but further light is thrown on the gentianose structure by the fact that some emulsin preparations split the gentianose molecule at a different point, producing sucrose and glucose. Assuming that the  $\gamma$ -fructose nucleus exists in the butylene-oxide form,\* this suggests that the full structure of gentianose can be written thus:—



## G.—SOME GLUCOSIDE CONSTITUTIONS

### 1. General

In the foregoing pages, an outline has been given of the methods by which the constitutions of the monosaccharides and the simpler polysaccharides can be investigated. The next series of compounds is the glucoside class with which the present

\* See p. 65.

section is concerned ; and here also it will be found that methylation has played the part of a master-reaction, since it has furnished the main evidence in the subject.

Any exhaustive study of a glucoside must include the following problems :—

I. The sugar and the non-saccharine constituent must be identified. This can be achieved by subjecting the glucoside to hydrolysis either with dilute acid or by the action of an enzyme.

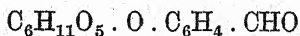
II. The mode of union between the sugar and the remainder of the glucoside must be determined. In cases where the non-saccharine constituent contains only a single hydroxyl group, no doubt can exist on this point ; but if the sugar be combined with a polyhydroxy-molecule, the complexity of the problem is considerably increased.

III. Since glucosides exist in  $\alpha$ - and  $\beta$ -forms, the configuration of the material under examination must be ascertained. This question can generally be answered by a study of the action of emulsin on the glucoside, since this enzyme is apparently a specific enzyme for  $\beta$ -alkylglucosides. If emulsin hydrolyses the given glucoside, it is fairly safe to infer that the glucoside is derived from  $\beta$ -glucose.

IV. After settling these three points, there still remains the investigation of the cyclic grouping in the sugar nucleus ; and it is with this last problem that we are mainly concerned here.

## 2. *Salicin*

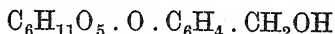
Our knowledge of the intimate constitution of salicin is due to the work of Irvine and Rose.<sup>1</sup> When salicin is hydrolysed by emulsin, it yields glucose and saligenin (salicylic alcohol). This proves that it is the glucoside of saligenin and, further, that it is a  $\beta$ -glucoside, since it is sensitive to emulsin. Since saligenin contains a phenolic hydroxyl as well as a primary alcoholic radicle, it is evident that the sugar has two possible points of attack during the formation of the glucoside from its constituents. The choice between these is easily made. When the glucoside salicin is oxidized with nitric acid, it yields helicin which is the glucoside of salicylic aldehyde :—



<sup>1</sup> Irvine and Rose, *J.*, 1906, 89, 814.



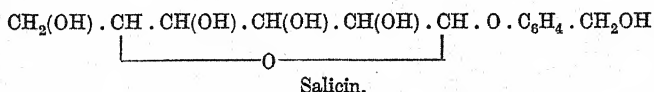
- Obviously, from this evidence, salicin must contain a primary alcoholic group which is oxidized to the aldehyde radicle; and hence it must be inferred that the primary alcoholic group is present in salicin. This implies that the linkage in the glucoside is through the phenolic oxygen; and the structure of salicin must therefore be



Irvine and Rose methylated salicin and obtained a pentamethyl-salicin. The obvious succeeding step would seem to be the hydrolysis of this substance and an identification of the tetramethyl-glucose which must thus be obtained; but unfortunately owing to the properties of the pentamethyl-derivative, this method broke down. Irvine and Rose solved the problem in another way. From tetramethyl-glucose and salicylic alcohol, they prepared a synthetic glucosidal product and on methylating this in turn, they obtained a pentamethyl-glucoside identical in every respect with the pentamethyl-derivative produced by methylating natural salicin.

This establishes the fact that the glucose nucleus in salicin has the same oxide-ring as ordinary glucose, since methylation of the two compounds leads to the same end-product. And since it has been established in a foregoing section that the tetramethyl-glucose employed contains the amylenoxide ring, it is evident that this ring is also present in the salicin molecule.

The structure of salicin can therefore be expressed by the formula:—



### 3. Indican

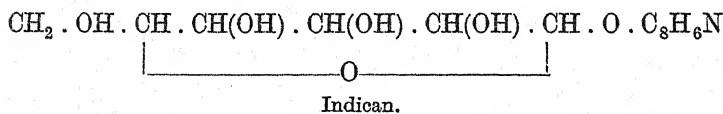
On hydrolysis, indican yields *d*-glucose and indoxyl. Macbeth and Pryde<sup>1</sup> have established the normal nature of the sugar structure by the following method. Indican was methylated by the silver oxide method and a tetramethyl-indican was thus formed. Now since the indoxyl part of the molecule might possibly be affected by the methylation, it was essential to prove that all the four methyl groups were attached to the sugar

<sup>1</sup> Macbeth and Pryde, *J.*, 1922, 121, 1660.

nucleus. For this purpose, the production of indirubin was utilized as a test. Baeyer<sup>1</sup> showed that indoxyl and isatin yield indirubin by condensation; and this reaction has been shown to be satisfactory as a method of estimation.<sup>2</sup> On submitting tetramethyl-indican to the reaction, Macbeth and Pryde found that indirubin was freely produced, proving that the methylation does not affect the indoxyl portion of the glucoside molecule.

In order to hydrolyse the methylated indican and isolate the methylated sugar, advantage was taken of a method devised by Irvine and Rose whereby the methylated glucoside is treated with methyl alcohol containing 1 per cent. hydrogen chloride. This reagent overcomes the somewhat stubborn resistance which these alkylated glucosides present to ordinary hydrolytic agents. As was to be expected, the product of the hydrolysis under these conditions was a mixture of  $\alpha$ - and  $\beta$ -tetramethyl-methylglucoside the indoxyl group being replaced by a methyl radicle.

Since the tetramethyl-methylglucosides obtained from indican are the same as those obtained by the methylation of the ordinary  $\alpha$ - and  $\beta$ -methylglucosides derived from glucose, it is evident that indican's sugar constituent has the same type of oxide-ring as glucose itself; and the formula of indican can be written thus:



#### 4. Arbutin

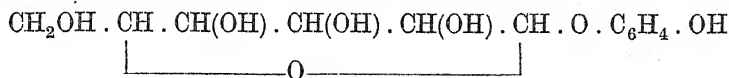
Macbeth and Mackay<sup>3</sup> have established by similar methods the existence of the normal amylenoxide ring in the glucoside arbutin. On hydrolysis, arbutin yields glucose and hydroquinone; and since it is attacked by emulsin, it must be regarded as a  $\beta$ -glucoside. On methylation with methyl sulphate and alkali, it yielded a pentamethyl-arbutin. Since on hydrolysis with 1 per cent. hydrogen chloride in methyl alcoholic solution, the

<sup>1</sup> Baeyer, *Ber.*, 1881, 14, 1745.

<sup>2</sup> Beyerinck, *Proc. K. Akad. Wetensch. Amsterdam*, 1899, 2, 120; Orchardson, Wood, and Bloxam, *J. Soc. Chem. Ind.*, 1907, 26, 4.

<sup>3</sup> Macbeth and Mackay, *J.*, 1923, 123, 717.

pentamethyl-arbutin liberated a mixture of  $\alpha$ - and  $\beta$ -tetramethyl-methylglucosides, it is evident that the methylated arbutin has one methyl group in the hydroquinone nucleus and four methyls in the sugar portion, for hydrolysis does not remove methyls attached to the normal hydroxyl groups of the sugars. On examination, the tetramethyl-glucose obtained by the hydrolysis of the methylglucoside mixture was found to be identical with the tetramethyl-derivative yielded by ordinary *d*-glucose. This proves that the normal amylenoxide structure is present in arbutin, which therefore must have the formula :

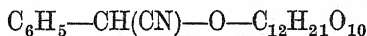


Arbutin.

This inference is confirmed by the fact that Macbeth and Mackay succeeded in synthesizing from tetramethyl-glucose and hydroquinone monomethyl-ether a pentamethyl-arbutin identical with that obtained from natural arbutin by methylation.

### 5. Amygdalin

The present survey of the glucosides may be closed with an account of the synthesis of amygdalin.<sup>1</sup> Amygdalin occurs naturally in bitter almonds and has the composition expressed by  $\text{C}_{20}\text{H}_{27}\text{O}_{11}\text{N}$ . On treatment with zymase, it is split up into one molecule of glucose and one molecule of *l*-mandelonitrile-glucoside, from which the single remaining glucose molecule can be removed by hydrolysis with emulsin. This behaviour suggests that amygdalin contains a biose and that its structure can be represented thus :—



The biose has been found<sup>2</sup> to be gentiobiose, the structure of which has been elucidated in an earlier part of this chapter.

When glucose is treated with emulsin, gentiobiose is formed.<sup>3</sup> By the action of acetic anhydride saturated with hydrogen bromide, Campbell and Haworth converted gentiobiose into hepta-acetyl- $\beta$ -bromo-gentiobiose by simultaneous bromination and acetylation. This product was condensed with *dl*-mandelic

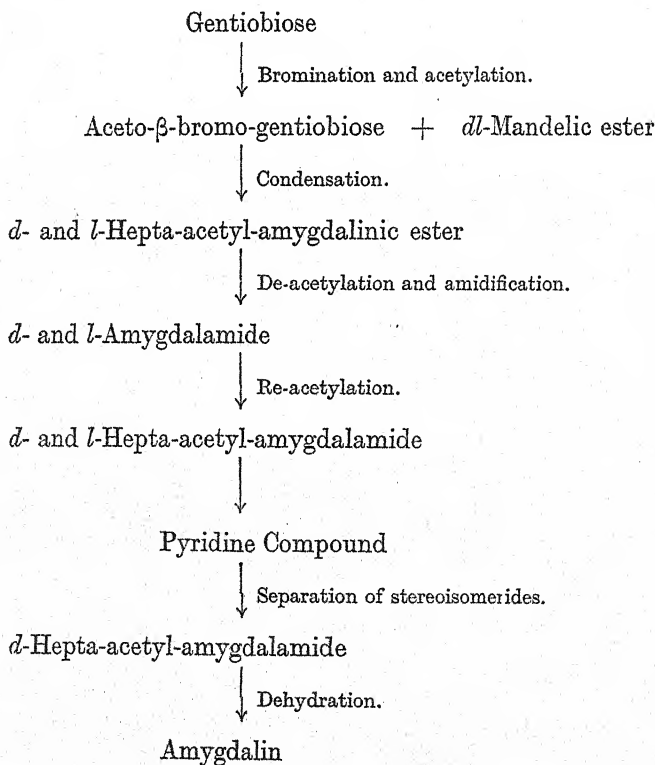
<sup>1</sup> Campbell and Haworth, *J.*, 1924, 125, 1337.

<sup>2</sup> Haworth and Wylam, *J.*, 123, 3120.

<sup>3</sup> Bourquelot, Hérissé, and Coirre, *Compt. rend.*, 1913, 157, 732.

ethyl ester in presence of silver oxide ; and the resulting material was identified as hepta-acetyl-*dl*-amygdalinic ethyl ester. From it, the amide of amygdalinic acid was prepared by the action of alcoholic ammonia, the acetyl groups being split off during the amide-formation. Re-acetylation in presence of pyridine yielded a pyridine compound with hepta-acetyl-amygdalamide ; and the stereoisomeric forms were separated from each other by fractional crystallization. Water was then removed from the acetylated amide by digestion with phosphoric oxide in xylene solution ; and in this way hepta-acetyl-amygdalin was obtained, from which amygdalin itself can be prepared by de-acetylation with alcoholic ammonia.<sup>1</sup>

As this series of reactions is rather difficult to follow, a table may be useful to indicate their inter-relationship.



<sup>1</sup> Fischer and Bergman, *Ber.*, 1917, 50, (B), 1065.

## CHAPTER III

### SOME POLYSACCHARIDES

#### A.—INULIN

##### 1. General

AMONG the reserve-materials of certain plants, the compound inulin<sup>1</sup> occupies an important position. It is a faintly reducing compound and yields only fructose when it is hydrolysed. It differs from starch in various ways, one or two of which may be mentioned here. With iodine, starch gives the well-known starch-iodine blue colour; whereas inulin has no such property. Starch is decomposed to maltose by diastase; but inulin is stable in presence of diastase. Starch is much less rapidly hydrolysed than inulin when dilute acids are employed; and the end-product of the hydrolysis is *d*-glucose instead of being *d*-fructose as in the case of inulin.

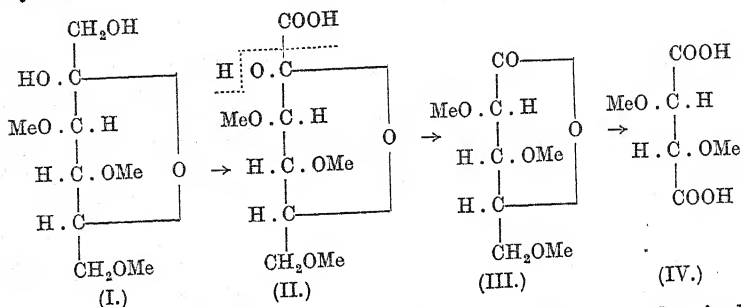
##### 2. The Constitution of Inulin

When inulin was treated with methyl sulphate, the reaction progressed in one stage to the formation of a dimethyl-inulin corresponding to the formula  $[C_6H_8O_3(OMe)_2]_n$ ; and a further operation was required to obtain the final product, trimethyl-inulin,  $[C_6H_7O_2(OMe)_3]_n$ . On hydrolysis with 1 per cent. oxalic acid at 100° C., trimethyl-inulin was converted smoothly into trimethyl-fructose,\* which appeared to belong to the  $\gamma$ -series.

<sup>1</sup> Irvine and Steele, *J.*, 1920, 117, 1474; Irvine, Steele and Shannon, *J.*, 1922, 121, 1060; Karrer and Lang, *Helv. Chim. Acta*, 1921, 4, 249; Haworth and Learner, *J.*, 1923, 619; Drew and Haworth, *ibid.*, 2690; Freudenberg *et al.*, *Ber.*, 1928, 61, [B], 1735; Pringsheim *et al.*, *ibid.*, 2018; 1929, 62, [B], 2378; *Annalen*, 1928, 462, 231; Schlubach and Elsner, *Ber.*, 1928, 61, [B], 2358; 1929, 62, [B], 1493.

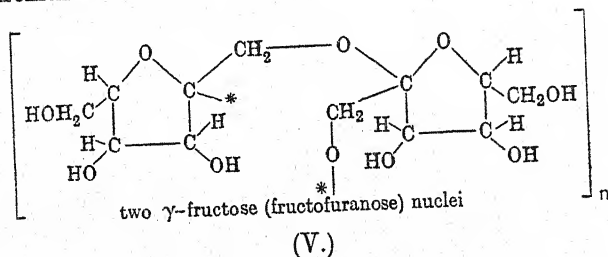
\* The yield of trimethyl-fructose from trimethyl-inulin exceeds 90 per cent. which seems to prove beyond doubt that all the fructose units of inulin are of the  $\gamma$ -type.

The constitution of this fructose derivative was established by a series of reactions indicated in the formulæ below :



The trimethyl-fructuronic acid (II.) was proved to be identical with the trimethyl-fructuronic acid derived from sucrose, so that obviously both inulin and sucrose contain the same kind of fructose ( $\gamma$ -fructose). The positions of the methyl-groups can be established by working back from the final *l*-dimethoxy-succinic acid (IV.); and since this proves that in the original inulin molecule the hydroxyl groups in positions 1 and 2 are not methylated, it is clear that these groups are involved in the linking together of the various fructose nuclei from which inulin is built up.

The general formula for inulin which would comply with these requirements is this :—

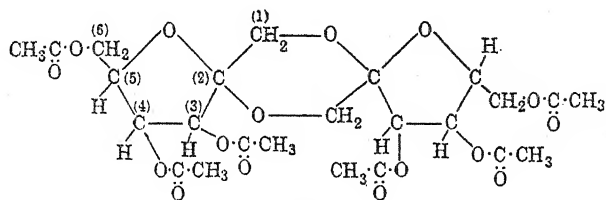


wherein the two valencies indicated by asterisks are assumed to link still further  $\gamma$ -fructose units to the complex in the same fashion.<sup>1</sup>

Inulin is a faintly reducing substance and is readily hydrolysed by the mildest acid reagents. Depolymerization takes place in various other solvents, and molecular weight

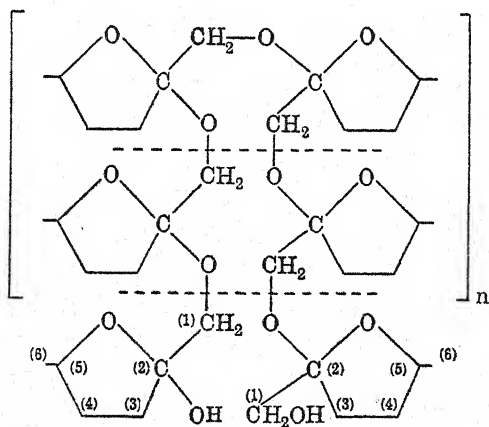
<sup>1</sup> Haworth and Learner, *J.*, 1928, 619.

determinations in such mediums as molten acetamide and liquid ammonia point to the complete rupture to a difructose compound. From acetylated inulin an 80 per cent. yield of hexa-acetyl difructose anhydride (VI.) has been obtained.<sup>1</sup>



(VI.)

The facts are conveniently explained by formulating the inulin molecule as an open double chain (VII.); open, to account for the faint reducing power, and double, to explain the ready formation of difructose compounds by scission at the oxygen links.<sup>2</sup>



(VII.)

The construction of a model of either difructose or trifructose will make it clear, however, that the stereochemical arrangements cannot be represented by a flat model.

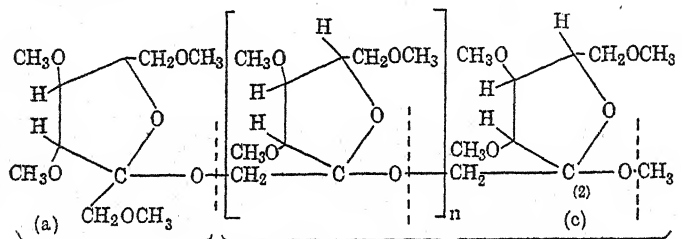
<sup>1</sup> Bergmann and Knebe, *Annalen*, 1926, 449, 302; Bergmann, *Ber.*, 1926, 59, 2079.

<sup>2</sup> Haworth, Hirst and Percival, *J.*, 1932, 2384.



## 3. The Molecular Size of Inulin

The end-group method of determining molecular size, which proved so useful in the case of cellulose,\* has also been successfully applied to methylated inulin.<sup>1</sup> In the preparation of methylated inulin all the reactions were carried out under the mildest possible conditions, and precautions were taken to test the homogeneity of the products obtained at different stages. From the final products of hydrolysis 1:3:4:6-tetramethyl fructofuranose ( $\gamma$ -fructose) was isolated in a quantity equivalent to 3.7 per cent. of the weight of inulin used. If methylated inulin be represented as the open chain compound (VIII.) composed of methylated fructofuranose units joined through oxygen at the positions 1 and 2 of the fructofuranose residues, it will be clear from inspection of the formula how the tetramethyl compound is produced.



Hydrolysis to  
1:3:4:6-Tetramethyl  
fructofuranose.

Hydrolysis to 3:4:6-Trimethyl fructofuranose  
and methyl alcohol.

(VIII.)

This isolation of tetramethyl fructofuranose establishes the nature of one of the molecular chain terminal groups. The action of inulin on Fehling's solution along with its instability in contact with alkali points to the presence of a free reducing group (2) (c) (VIII.) at the other terminal residue. In addition the quantitative separation of the tetramethyl compound permits the molecular chain length to be calculated as approximately 30 fructofuranose units, corresponding to a molecular weight of about 5,000. This value agrees very well with that estimated from osmotic pressure measurements.<sup>2</sup>

\* See p. 88.

<sup>1</sup> Haworth, Hirst and Percival, *loc. cit.*

<sup>2</sup> Carter and Record, *J. Soc. Chem. Ind.*, 1936, 218.

## B.—CELLULOSE

## 1. General

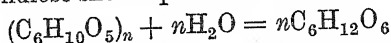
The problem of cellulose's constitution bristled with difficulties. Owing to the insolubility of the material in ordinary solvents, chemical purification is beset with quite abnormal troubles. The colloidal character of the material throws out of account any normal method of ascertaining the molecular weight. And the possibility that intramolecular change or degradation will follow the use of even mild reagents adds to the obstacles in the way of investigators. Difficulties have, however, been overcome one by one. The adoption of Haworth's 1:5-glucopyranose formula for glucose; careful study of the products of methylation, acetylation and hydrolysis; a more extended use of physical methods and the rejection of certain structural ideas have gradually narrowed down the issue and given clearer views of the molecular structure. Complex substances of high molecular weight resulting from condensation or polymerization of simpler units may exist in three principal molecular forms. The linear type is the simplest and includes spiro chains and their modifications. The second possibility is large ring molecules,\* and here the rings may exist in diverse shapes, varying from open patterns to collapsed elongated parallel closed systems related in form to the linear type of molecule. Lastly there is the network or cross-linked type, which obviously can be the most complex of the three groups. Cellulose is now classified as a linear type of molecule. As well as the problem of molecular structure there is an additional interest in cellulose. This material and its derivatives in the organized or oriented forms of wood, paper, textiles, plastics, lacquers and films play a prominent part in modern civilization, and it, therefore, becomes a matter of practical importance to study the orientation of the cellulose in the larger units, the micelles, and to examine the property they possess, to an outstanding degree, of forming strong fibrils and films.

## 2. The Constitution of Cellulose.

A normal cotton cellulose is represented by the formula  $(C_6H_{10}O_5)_n$ , and the facts that glucose has been obtained in

\* See Vol. I, p. 79.

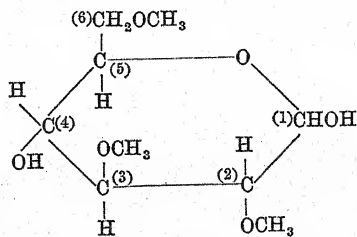
90.67 per cent. yield as the end-product of hydrolysis with sulphuric acid,<sup>1</sup> and in the form of a mixture of  $\alpha$ - and  $\beta$ -methyl-glucosides in 95.5 per cent. yield,<sup>2</sup> leave no doubt that cotton cellulose is essentially composed of glucose units. A complete hydrolysis of cellulose should proceed according to the equation :



In determining the manner in which the various monose nuclei are linked together in the polysaccharide structure, methylation has proved an indispensable weapon. Discarding the silver oxide method,\* Denham and Woodhouse<sup>3</sup> discovered that methyl groups can be introduced very simply by impregnating cellulose with 15 per cent. solution of sodium hydroxide and then applying methyl sulphate. The process was found to take place in stages, more methyl groups being introduced with each successive treatment of the material.

Denham and Woodhouse<sup>4</sup> found that their methylated celluloses when subjected to the action of hydrolysing agents, did not lose the methyl radicles; so that in this way a new line of attack on the cellulose problem was laid open. On subjecting to hydrolysis a methylated cellulose containing 25 per cent. of methoxyl, a trimethyl-glucose was isolated among the reaction-products; and thus a definite reference-compound was obtained.

Denham and Woodhouse were able to identify this crystalline trimethyl-glucose as the 2:3:6-derivative; so that, adopting the pyranose structure,<sup>5</sup> its constitution is expressed by



(I.)

<sup>1</sup> Monier-Williams, *J.*, 1921, 119, 803.

<sup>2</sup> Irvine and Hirst, *J.*, 1922, 121, 1585.

<sup>3</sup> Denham and Woodhouse, *J.*, 1913, 103, 1735; Denham, *J.*, 1921, 119, 77.

<sup>4</sup> Denham and Woodhouse, *J.*, 1917, 111, 244.

<sup>5</sup> Haworth, *Nature*, 1925, 116, 430; Drew and Haworth, *J.*, 1926, 2303; Haworth, *The Constitution of Sugars*, (1929), pp. 34-40.

\* See p. 44.

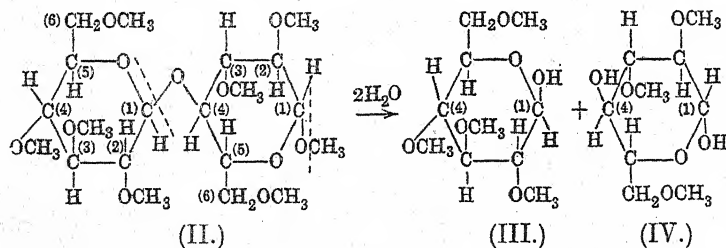
A glance at this formula will show that the positions 1 and 4 in the molecule have not borne free hydroxyl groups during the methylation of cellulose; and therefore these two points must be the positions at which the remaining parts of the cellulose molecule are linked on.

It has been demonstrated that 2:3:6-trimethylglucose can be obtained in approximately 79 per cent. yield from cotton cellulose after methylation and hydrolysis.<sup>1</sup>

A further glimpse of the cellulose constitution is gained from cellobiose. This disaccharide is related to cellulose as maltose is to starch, and is obtained from cellulose by incomplete hydrolysis either by means of acetic anhydride and concentrated sulphuric acid (acetolysis) or else by bacterial action.<sup>2</sup>

Cellobiose is obviously composed of two glucose nuclei; and for the present purpose the essential point is the manner in which these are linked. To solve this problem, the methylation method was employed by Haworth and Hirst<sup>3</sup>; and by using in succession methyl sulphate and the silver oxide method, they obtained a heptamethyl-methylcellobioside. On hydrolysis, this last compound yielded two substances which are now known to be 2:3:4:6-tetramethyl-glucose (III.) and 2:3:6-trimethyl-glucose (IV.).

From these fragments, the structure of heptamethyl-methylcellobioside (II.) can be reconstituted in the following form: \*



From this structure it appears that the 2:3:6-trimethyl-glucose fragment is linked to the rest of the molecule through hydroxyl

<sup>1</sup> Irvine and Hirst, *J.*, 1923, 518.

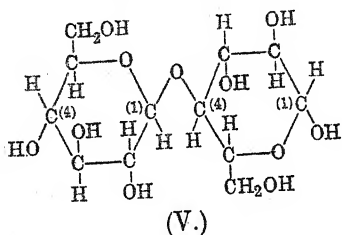
<sup>2</sup> Pringsheim, *Z. physiol. chem.*, 1912, 78, 266.

<sup>3</sup> Haworth and Hirst, *J.*, 1921, 119, 193; 1926, 129, 1858; Charlton, Haworth and Peat, *ibid.*, 89; compare Zemplén, *Ber.*, 1926, 59, 1254.

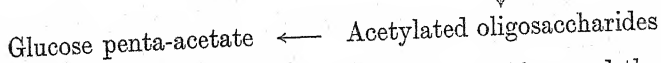
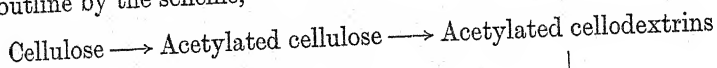
\* It is evident from this that cellobiose is identical in structure with maltose. Maltose is a glucose-α-glucoside, whereas cellobiose is a glucose-β-glucoside.

group 4; and this is the important point so far as the present argument is concerned. Since cellobiose is an intermediate degradation compound between cellulose and glucose, and has been obtained in considerable yield from cellulose, it is concluded that cellulose also contains this cellobiose linking.

Cellobiose is hydrolysed by the enzyme  $\beta$ -glucosidase of emulsin and not by maltase ( $\alpha$ -glucosidase), and consequently the  $\beta$ -glucoside structure (V.) is assigned to it.



In addition to cellobiose the more complex oligosaccharides, cellotriose, cellotetraose and cellohexaose<sup>1</sup> have been isolated from cellulose by acetolysis and by hydrolysis, as well as cello-dextrin, which is regarded as a mixture of compounds containing sixty and more carbon atoms in the molecule. The degradation of cellulose by acetolysis may, therefore, be represented in broad outline by the scheme,

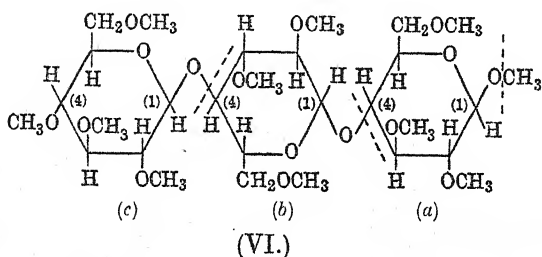


Taking into consideration the structure of cellobiose and the nature of the other products of decomposition of cellulose, it is probable that the molecule is composed of glucose units uniformly linked together as in the  $\beta$ -glucoside form of cellobiose. This view finds further support from work on trimethylcellulose.<sup>2</sup> Pure trimethylcellulose when submitted to acetylosis at 15° C and then simultaneously deacetylated and methylated yielded

<sup>1</sup> Bertrand and Benoist, *Compt. rendu.*, 1923, **176**, 1583; **177**, 85; Irvine and Robertson, *J.*, 1926, **129**, 1488; Zemlén, *Ber.*, 1926, **59**, 1254; Zemlén *et al.*, *Ber.*, 1936, **69**, 1827; Zechmeister and Toth, *Ber.*, 1931, **64** [B], 854; 1933, **66**, 269.

<sup>2</sup> Haworth, Hirst and Thomas, *J.*, 1931, 824.

tetramethyl-methylglucoside, heptamethyl- $\beta$ -methylcellobioside, decamethyl- $\beta$ -methylcellotrioside (VI.), and a fourth compound which was probably a cellotetraose derivative. The cellotrioside was demonstrated to be structurally similar to cellobiose and yielded on hydrolysis tetramethyl-glucose and 2 : 3 : 6-trimethyl-glucose in the proportions of 1 : 2. Representing the cellotrioside (VI.) as a  $\beta$ -linked compound, inspection of the formula will show how it may yield on hydrolysis tetramethyl-glucose and 2 : 3 : 6-trimethyl-glucose in the proportions mentioned. It will be borne in mind that on hydrolysis the methyl-glucoside group at position (1) in ring (*a*) is split off, and that the methyl group at position (4) in ring (*c*) is not glucosidic.



Decamethyl- $\beta$ -methylcellotrioside has been synthesized from 2 : 3 : 6-trimethyl- $\beta$ -methylglucoside and heptamethyl-cellobiose-1-chlorohydrin,<sup>1</sup> leaving very little doubt that the  $\beta$ -linkage occurs throughout the cellulose molecular chain. Finally, in this connection the study of certain physical properties of cellulose and its derivatives supports the results of chemical examination. X-ray analysis of cellulose indicated a recurring unit  $10.3\text{\AA}$  along the fibre axis, which agrees almost exactly with the length calculated for the cellobiose unit.<sup>2</sup> Measurements of the optical rotation and observations on the progress of hydrolysis of cellulose and its degradation compounds give further evidence of the uniformity of the molecular linkages in cellulose.<sup>3</sup>

<sup>1</sup> Freudenberg and Nagai, *Ann.*, 1932, 494, 63.

<sup>2</sup> Sponsler and Dore, *Colloid Symposium Monograph*, N.Y., 1926, 174; Meyer and Mark, *Ber.*, 1928, 61, [B], 593; Meyer and Misch, *Helv. Chim. Acta*, 1937, 20, 235.

<sup>3</sup> Freudenberg, Friedrich and Bumann, *Ann.*, 1932, 494, 41; Kuhn, *Ber.*, 1930, 63, 1503; Freudenberg *et al.*, *Ber.*, 1930, 63, 1510; 1935, 68, 2070.



3. *The Molecular Size and Shape of Cellulose*

When dealing with macromolecular substances the ordinary methods of determining molecular weights are uncertain, and information must be sought in other directions. It is an open question whether or not the molecular chains of native cellulose are uniform in length. It is possible that the lengths of the chains may vary within wide limits, from very long in native cellulose through all intermediate stages of degradation until finally the oligosaccharides and glucose are reached. So that for any particular specimen of purified cellulose the molecular weight obtained is likely to be an average value. The most acceptable results have been obtained by means of end-group determinations,<sup>1</sup> ultracentrifugal analysis,<sup>2</sup> viscosity<sup>3</sup> and osmotic pressure measurements,<sup>4</sup> but there is still lack of agreement in the results obtained. The end-group method of determining molecular size is, in contrast with the physical methods, independent of solution characteristics such as association and solvation, and depends upon the chemical structure of the substance. The possibility of degradation during the preparation for analysis, however, cannot be ignored. In the case of cellulose it has been pointed out by Haworth and Machemer<sup>5</sup> that if the molecule exists as a long chain the end-groups should be recognizable by their special properties, the reducing group at one end and the tetrahydroxyglucose residue at the other. On the other hand if the molecule were in the form of a large ring all the C<sub>6</sub> units would be identical in properties. To test this idea, carefully prepared methylated cellulose obtained from acetone-soluble cellulose acetate was hydrolysed at low temperature, and the methylated glucose components produced converted into

<sup>1</sup> Haworth and Machemer, *J.*, 1932, 2270; Bergmann and Machemer, *Ber.*, 1930, 63, 316, 2304; Schmidt, Jandebeur *et al.*, *Ber.*, 1936, 69, [B], 366.

<sup>2</sup> Svedberg, *Kolloid-Z.*, 1925, 36 (Zsigmondy Festschr.), 53; Svedberg and Nicols, *J. Amer. Chem. Soc.*, 1927, 49, 2920; Svedberg, *Z. physik. Chem.*, 1927, 127, 51; Stamm, *J. Amer. Chem. Soc.*, 1930, 52, 3047; Lansing and Kraemer, *J. Amer. Chem. Soc.*, 1935, 57, 1369; *J. Physical Chem.*, 1935, 39, 153.

<sup>3</sup> Staudinger, Ritzenthaler and Kautz, *Ber.*, 1935, 68, [B], 1225; Staudinger, *ibid.*, 474; von Ekenstein, *Ber.*, 1936, 69, 549; Staudinger, *Cellulosechem.* 1934, 15, 53, 65.

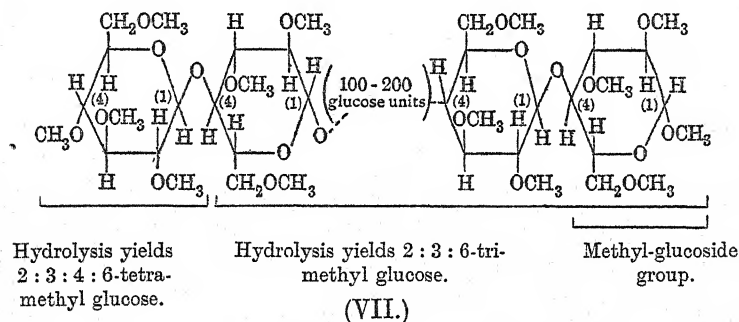
<sup>4</sup> Herzog and Herz, *Trans. Faraday Soc.*, 1933, 29, 57; Carter and Record, *J. Soc. Chem. Ind.*, 1936, 218.

<sup>5</sup> *J.*, 1932, 2270.



the methyl glucosides. From the glucosides by exhaustive fractional distillation 2:3:4:6-tetramethyl-methylglucoside was separated from 2:3:6-trimethyl-methylglucoside in a yield that represented 0.6 per cent. of the methylated cellulose taken. This detection and estimation of tetramethyl-methylglucose points clearly to the existence of open chain molecules, and permits a calculation of the molecular chain length to be made. It is concluded that the chain length is not less than 100 and not more than 200  $\beta$ -glucose units corresponding to a molecular weight of 20,000–40,000.

Inspection of the diagram representing methylated cellulose (VII.) and its products of hydrolysis will make these points clearer.



These values for the molecular weight are in agreement with those calculated from measurements of X-ray diffraction patterns of the materials. Very slight hydrolysis at any stage in the preparation of the methylated cellulose would affect the result very considerably, and it has been shown that, depending on the method of preparation employed, the estimated chain length varies within wide limits. Thus when air is replaced by an atmosphere of nitrogen during methylation of the cellulose no tetramethyl-methylglucoside could be detected by the end-group process.<sup>1</sup>

The values obtained from viscosity measurements are in the neighbourhood of 120,000–180,000, and those from ultra-centrifugal analysis vary from 56,000 to 300,000.

<sup>1</sup> Haworth *et al.*, *J.*, 1939, 1885.

## C.—STARCH

## 1. General

Starch is very widely distributed in the vegetable world and forms the most important reserve food material of plants. The method of isolating starch depends on the raw material used; from potatoes, fine-grinding, to break down the cells, is followed by thorough washing with water on sieves to retain protein and cellulose materials; from wheat flour, suspension in water and fermentation of the gluten permits the removal, by solution, of the products of degradation. Further purification can be effected by repeatedly freezing a dilute colloidal solution<sup>1</sup> or by treating the starch with alcoholic hydrogen chloride.<sup>2</sup> Starch grains are insoluble in cold, but rupture with gelatinization in hot water. This swelling of the grains can also be brought about by chemical reagents such as dilute solutions of caustic soda, ammonium thiocyanate or chloral hydrate.<sup>3</sup>

2. The Isolation of Amylose ( $\beta$ -Amylose) and Amylopectin ( $\alpha$ -Amylose)

It was first pointed out by Nägeli that the natural grains of starch contained two independent materials.<sup>4</sup> These are now generally known as amylose and amylopectin. There are differences of opinion as to the distribution of the substances in the starch grain. On the one hand it is held that amylopectin forms the outer cover of the grain with the amylose inside, on the other hand it is contended that the two compounds are distributed throughout the grain, and that the apparent enveloping nature of amylopectin is due to its colloidal properties; the action of hot water or other swelling agent causing it to gel and immesh the soluble amylose. The components of a starch solution may be selectively precipitated by solutions of alcohol of different strengths, and this was the basis of the first successful chemical method of separation. A 3 per cent. starch solution

<sup>1</sup> Malfitano and Moschkoff, *Compt. rend.*, 1910, 151, 817.

<sup>2</sup> Taylor and Nelson, *J. Amer. Chem. Soc.*, 1920, 42, 1726.

<sup>3</sup> Reychler, *Bull. Soc. chim. Belg.*, 1920, 29, 118.

<sup>4</sup> *Die Stärkekörner*, Zurich, 1858.

and a 40 per cent. sodium carbonate solution were mixed and 95 per cent. alcohol added. The amylopectin precipitated was purified by washing and dialysis.<sup>1</sup>

The amyloses may be separated by a variety of other methods, chemical, biochemical and physical. The alternate warming and freezing of dilute gelatinized starch suspensions followed by filtration and precipitation of the dissolved amylose has proved a satisfactory method, and by modifying these conditions somewhat amylopectin may also be isolated in a pure condition.<sup>2</sup> On account of the colloidal nature of amylopectin it is possible to bring about the final separation by centrifugal sedimentation or ultrafiltration.<sup>3</sup> Electrodialysis has also been advantageously employed. Colloidal amylopectin has a relatively strong negative charge associated with it and migrates readily under the influence of an electric current.<sup>4</sup>

Under carefully controlled conditions barley diastase attacks starch, converting the amylose present into maltose, whilst the amylopectin is scarcely affected. The maltose may be removed by dialysis and the amylopectin recovered by one of the known methods.<sup>5</sup>

### 3. *The Disaggregation and Degradation Products of Starch*

There are three principal methods of breaking down starch aggregates and molecules: by heat, by mineral acids, and by enzyme action. By one or other method of attack starch can be converted into the following products, which are placed in order of increasing simplicity: (1) soluble starches, (2) dextrins, (3) maltose, (4) glucose and glucose compounds. The end-product of acid hydrolysis of starches, dextrins, and maltose, is glucose and, provisionally, it may be assumed that these molecules are built up of glucose units.

<sup>1</sup> Gatin-Gruzewska, *Compt. rend. Soc. Biol.*, 1908, 64, 178; *Compt. rend.*, 1908, 146, 540.

<sup>2</sup> Baldwin, *J. Amer. Chem. Soc.*, 1930, 52, 2907.

<sup>3</sup> Fouard, *Comp. rend.*, 1908, 146, 285, 978; Gatin-Gruzewska, *ibid.*, 1908, 146; Nelson and Morgan, *J. Biol. Chem.*, 1923, 58, 305; Taylor and Iddles, *Ind. Eng. Chem.*, 1926, 18, 713; Baird, Haworth and Hirst, *J.*, 1935, 1201.

<sup>4</sup> Samec, *Kolloidchem. Beitr.*, 1914, 6, 23; 1915, 7, 137; 1919, 10, 289; 1920, 12, 281; 1921, 13, 272; Taylor and Iddles, *loc. cit.*

<sup>5</sup> Ling and Nanji, *J.*, 1923, 123, 2666.

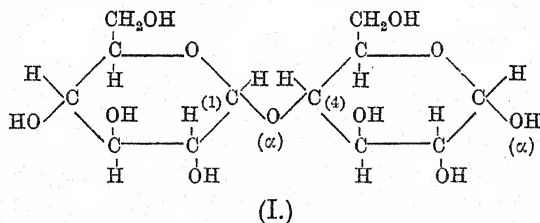
The substance commonly called soluble starch may be prepared by treating a starch suspension with acid or an oxidizing agent. The change is not extensive as soluble starch resembles raw starch in being granular in shape, practically insoluble in cold water, and in giving the characteristic colour reaction with iodine. The most important technical difference between the two is that soluble starch forms a much thinner hot solution with water. It is considered that the first effect of mild action on raw starch is to break down the colloidal aggregates, leaving the chemical molecules intact. More drastic action degrades the molecules to dextrans and finally to sugars. Very definite evidence has been brought forward to show that soluble starch formed under mild conditions is a disaggregation product of raw starch.<sup>1</sup> Potato starch was heated at 80° C. for thirty minutes with a very dilute alcoholic solution of hydrogen chloride. The product, whilst behaving similarly to starch in its iodine reaction and to polarised light, readily dissolved in hot water, giving mobile solutions, and could be converted into a form soluble in cold water. This soluble starch or simplified amylose when air-dried and kept for some hours reverted to an insoluble form similar, in every way to ordinary starch. It was concluded that this specimen of starch, previously soluble in cold water, had undergone reaggregation to a higher complex. The simplified amylose, freshly prepared, was subjected to the end-group method of analysis\* to determine its molecular weight. The value obtained was 5,000, agreeing exactly with that obtained by the same method for ordinary starch. In addition, the simplified amylose when methylated and examined viscosimetrically by Staudinger's method, had approximately the same molecular size.

The term dextrin may be regarded as including the degradation products of starch lying between soluble starch and saccharides in molecular size. Owing to the lack of constitutional information a certain amount of confusion has existed in the nomenclature of the dextrans. They have been classified as amylo-, erythro-, achroo- and maltodextrans chiefly on the basis of their optical rotatory power, iodine colour reaction and reducing power. It is probable that each group includes a number

<sup>1</sup> Baird, Haworth and Hirst, *J.*, 1935, 1201.

\* See p. 88.

of compounds closely related in molecular size. More recently degradation products have been isolated and identified as containing 3, 4, 5, 6, 7, 9, 12 and 17 glucose units respectively.<sup>1</sup> The substance known as  $\alpha$ -amylodextrin is of considerable interest and was first isolated by the action of ungerminated barley diastase on starch.<sup>2</sup> It has recently been the subject of further investigation.<sup>3</sup> The enzyme of ungerminated grain is now known as  $\beta$ -amylase and the name  $\alpha$ -amylodextrin now refers to the dextrin formed when the action of  $\beta$ -amylase on starch is allowed to proceed to completion. This action goes on until approximately 50 per cent. of the starch is converted into maltose. This formation of maltose may be envisaged as taking place step by step along the molecule from the non-reducing end until a point of resistance is met and enzyme action ceases, the molecular residue being  $\alpha$ -amylodextrin.<sup>4</sup> The dextrin has been converted into methyl dextrin directly and through the acetate. The chain length determined by the end-group method of analysis in each case was found to be 11-12 glucose units. It has been claimed that the action of malt diastase on amylose gives a quantitative yield of maltose,<sup>5</sup> and as is well known the end-product of acid hydrolysis of starch and the dextrins is glucose. The production of maltose in quantity is important as it provides valuable evidence of the structure of the starch molecule. Maltose is glucopyranose-4- $\alpha$ -glucopyranoside (I).\*



<sup>1</sup> Freudenberg and Friedrich, *Naturwiss.*, 1930, 18, 1114; Waldschmidt-Leitz and Reichel, *Z. physiol. Chem.*, 1934, 223, 76; Haworth, Hirst, and Waite, *J.*, 1935, 1299; Haworth, Hirst, Kitchen and Peat, *J.*, 1937, 791.

<sup>2</sup> Baker, *J.*, 1902, 81, 1177.

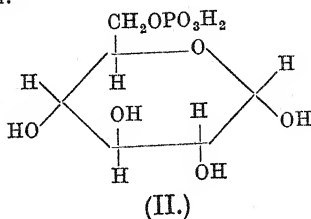
<sup>3</sup> Haworth, Hirst, and Waite, *loc. cit.*; Haworth, Hirst, Kitchen, and Peat, *loc. cit.*

<sup>4</sup> Hanes, *Canadian J. Res.*, 1935, 13, 185; *Proc. Roy. Soc.*, 1940, [B], 128, 421; 129, 174.

<sup>5</sup> Ling and Nanji, *J.*, 1925, 127, 639.

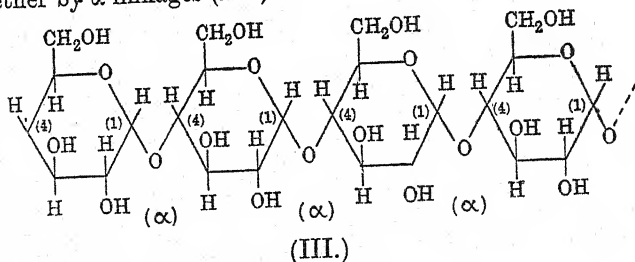
\* For proof of the structure of maltose, see p. 66.

In the examination of starch and its decomposition products, small amounts of phosphorus, nitrogen, silicon, and fatty acids have been detected and estimated. Phosphorus was at first thought to occur as part of traces of impurities which could not be eliminated. It has, however, been established that phosphorus is present in the molecule in combination as a phosphoric acid ester,<sup>1</sup> and glucose-6-phosphoric acid (II.) has been isolated from potato starch.<sup>2</sup>



#### 4. The Structures of Amylose and Amylopectin

It has been established that the molecules of both amylose and amylopectin are composed of chains of glucose units joined together by  $\alpha$ -linkages (III.).



Such molecules should yield on hydrolysis, glucose, maltose and dextrans of varying complexity.

The problem, therefore, that presents itself is: are the differences between the two substances purely physical or are they physical and chemical? From the facts it was at first thought that amylose and amylopectin differed chiefly in physical properties, and that the molecular group of 22 to 24 glucose units occurred in both substances.

<sup>1</sup> Fouard, *Institut Pasteur Ann.*, 1907, 21, 475; Semac and Hœfft, *Kolloid-chem. Beitr.*, 1913-14, 5, 141.

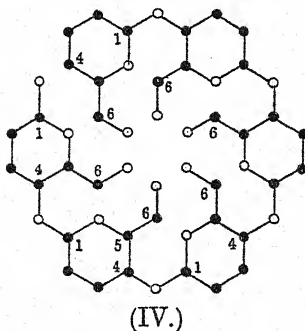
<sup>2</sup> Posternak, *Comp. rend.*, 1933, 197, 1157; 1934, 198, 506; *Arch. Sci. phys. nat.*, 1935, [V], 17, Suppl., 182.



Later work points to the amylose constituent of starch having an unbranched molecular chain made up of 240 to 300 glucose units.<sup>1</sup> Amylose from maize starch from quantitative estimations of its reducing groups appears to have a chain length of only 150 glucose units.

This linear or unbranched molecular form ascribed to amylose from its chemical behaviour is supported by physical evidence. It has been shown that amylose is capable of yielding strong pliable acetate films, and amylopectin on the other hand produces only weak brittle films. The pliable amylose acetate films on being stretched become birefringent with an increase of tensile strength. This behaviour is usually interpreted as being due to molecular orientation, and an indication of the linear nature of the molecules constituting the film. Similarly X-ray diffraction patterns taken during the stretching of these films indicate a progressive change from an amorphous to a highly crystalline state. When elongated to 400–600 per cent. the films produce a typical fibre pattern on exposure to X-rays. The presence of discrete spots on the diffraction pattern is evidence of a marked degree of orientation, and further supports the evidence that the molecules are of a chain nature.<sup>2</sup>

An interesting extension of work on the shape of starch molecules has been made. Some years ago from theoretical considerations it was shown that  $\alpha$ -glucose in molecular chain formation could take up a strainless hexagonal shape composed of six units (IV.) and in connection with the ready aggregation



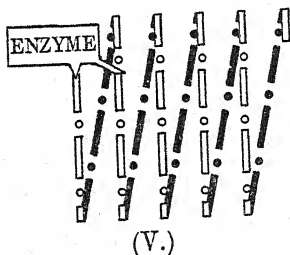
<sup>1</sup> Hess and Krajnc, *Ber.*, 1940, 73, 976; Meyer *et al.*, *Helv. Chim. Acta*, 1940, 23, 66, 864; 1941, 24, 378; Hassid and McCready, *J. Amer. Chem. Soc.*, 1943, 65, 1157.

<sup>2</sup> Whistler and Schieltz, *J. Amer. Chem. Soc.*, 1943, 65, 1436.



of some starches it was suggested that the existence of spiral molecules would account for this ease of entanglement.<sup>1</sup>

These ideas have been elaborated and the molecule visualized as a close spiral with six glucose units in each coil with the oxygen linkages of adjacent coils in close proximity<sup>2</sup> (V.). This formulation has been put forward to account for the enzymic production of considerable amounts of dextrans containing about six glucose units in the molecule. If it is assumed that there are two points of attachment and activity between the enzyme and the starch, the degradation is pictured as proceeding from the end of the starch molecule, hydrolysis occurring at the sixth and seventh units. In this way a two-point attachment of the enzyme adjacent to the oxygen linkages of the starch followed by hydrolysis would liberate one complete coil of the spiral in the form of a 6-unit dextrin.



A synthetic amylose containing 80 to 90 glucose units in the molecule has been prepared from glucose-1-phosphate by enzyme action (VI.). This substance is completely converted into maltose by  $\beta$ -amylase.

The amylopectin molecule has a more complex structure. The end-group method of determining the chain length shows the presence of one non-reducing terminal group in twenty-four to thirty glucose units. Molecular weight determinations by physical methods give very much higher values. These methods, however, have not yet been satisfactorily standardised.

It is concluded from its properties that the amylopectin molecule is a large one, and built up from these basal chains of

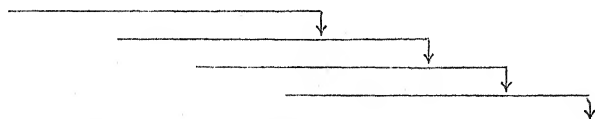
<sup>1</sup> Haworth, *The Constitution of Sugars*, 1929; Haworth, Hirst and Waine, *J.C.S.*, 1935, 1299.

<sup>2</sup> Hanes, *The New Phytologist*, 1937, XXXVI., 101, 189; Rundle and French, *J. Amer. Chem. Soc.*, 1943, 65, 1707; Rundle and Edwards, *ibid.*, 2200.

24 to 30 glucose units.<sup>1</sup> It has been shown that methylated starch on hydrolysis yields 2 : 3-dimethylglucose in approximately the same proportion as the end-group tetramethylglucose. It is consequently concluded that there is a 1 : 6-glycosidic linkage in the amylopectin molecule in addition to the 1 : 4-linkage of the units of the basal chains.

Further, this 1 : 6-linkage is of the  $\alpha$ -type as it undergoes hydrolysis by an  $\alpha$ -glucosidase, and is not affected by  $\beta$ -amylase.<sup>2</sup> The conclusions are supported by observations of the specific rotations of some limit dextrans.

All this evidence on the behaviour of amylopectin now permits a provisional representation of the molecule to be made (VI.).



(VI.)

In this laminated diagram each line represents a basal chain of 24 to 30 glucose units combined by  $\alpha$  1 : 4-linkages, and each arrow head indicates the union of the terminal reducing unit of one basal chain with the 6-position of a unit of a neighbouring chain.

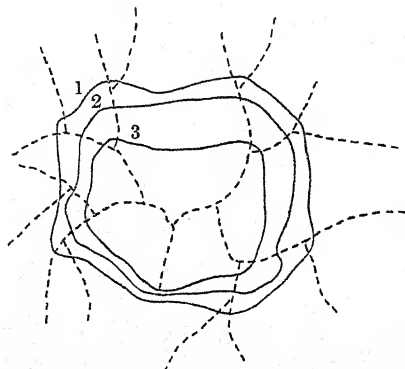
From the behaviour of amylopectin towards enzymes a more detailed structure of the molecule has been put forward.<sup>3</sup> As is known  $\beta$ -amylase does not completely degrade amylopectin, but leaves a residual dextrin which amounts to about 50 per cent. of the original material. End-group determinations on this dextrin showed the presence of about double the tetramethylglucose obtained from amylopectin. The residual dextrin can be further degraded by  $\alpha$ -glucosidase, and the dextrin left can now be hydrolysed by  $\beta$ -amylase to produce maltose and a

<sup>1</sup> Haworth, Hirst, and Oliver, *J.C.S.*, 1934, 1917; Hirst and Young, *ibid.*, 1939, 951, 1471; Hawkins, Jones, and Young, *ibid.*, 1940, 390; Haworth, *Chem. and Ind.*, 1939, 58, 917.

<sup>2</sup> Bawn, Hirst, and Young, *Trans. Faraday Soc.*, 1940, 36, 880; Haworth, Hirst, and Isherwood, *J.C.S.*, 1937, 577; Barker, Hirst, and Young, *Nature*, 1941, 147, 296; Freudenberg and Boppel, *Ber.*, 1938, 71, 2505; 1940, 73, 609.

<sup>3</sup> Meyer and Bernfeld, *Helv. Chim. Acta*, 1940, 23, 875.

simpler dextrin, which gives a light red-brown colour with iodine. To account for these results a ramified structure (VII.) containing both 1:4- and 1:4:6-linkages has been suggested. The dotted lines represent part of the amylopectin molecule, the continuous line marked 1 indicates the end-point of the initial attack by  $\beta$ -amylase, line 2 shows the points at which the hydrolysis by  $\alpha$ -glucosidase ends, and line 3 the end of further fission by  $\beta$ -amylase.

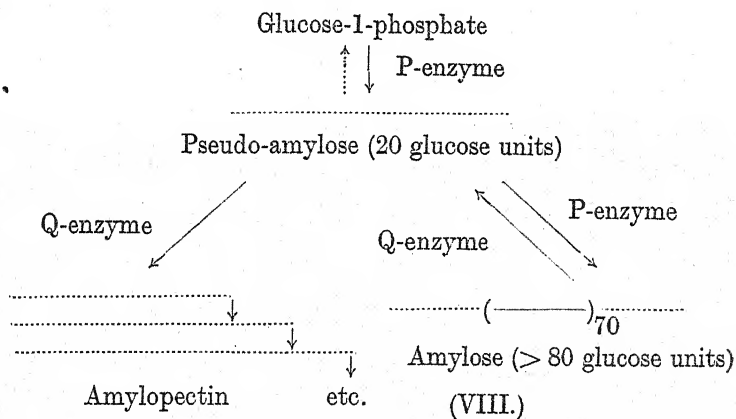


(VII.)

Important advances have been made in the field of enzymic synthesis and degradation of starch. It was discovered that an enzyme (P-enzyme) occurring in the potato and a number of other higher plants was capable of catalysing the synthesis of amylose from glucose-1-phosphate. This line of investigation has been extended and another enzyme, named the Q-enzyme, isolated and found capable of acting in conjunction with the P-enzyme to bring about the synthesis of amylopectin. This synthetic amylopectin has a number of properties identical with those of the natural substance. A working hypothesis of the course of the synthesis of whole starch in the plant has been suggested.

The synthesis of polyglucose from glucose-1-phosphate is a reversible reaction, the equilibrium being determined by the concentrations of the ions  $\text{HPO}_4''$  and  $\text{C}_6\text{H}_{11}\text{O}_5\text{OPO}_3''$ . The function of the P-enzyme is to bring about the formation of  $\alpha$ -1:4-glycoside linkages by the combination of molecules of

glucose-1-phosphate and the liberation of phosphate ions, and the reverse process of splitting these glycoside linkages in the presence of inorganic phosphate. Unbranched chains of glucose units are the result of the synthesis. The part played by the Q-enzyme appears to be the formation of 1:6-glucosidic linkages between chains of glucose units. In the absence of the Q-enzyme or when its concentration is below a critical value, P-enzyme produces amylose. When both P- and Q-enzymes are present in suitable proportions, the normal amylose synthesis is interrupted when an average chain length of about 20 glucose units is reached, and the Q-enzyme proceeds to catalyse the attachment of these chains to one another by 1:6-unions, yielding the laminated amylopectin structure. The Q-enzyme also possesses an amylose-hydrolysing function.<sup>1</sup> These ideas are illustrated in the diagram (VIII.).



The recent advances made in our knowledge of the structure of the starch molecule have been rapid and extensive, largely owing to the outstanding contributions of W. N. Haworth and his collaborators. The perfecting of the end-group method of assay was an important addition to polysaccharide chemistry, and the ideas put forward from time to time on the nature of the starch molecule have stimulated further research and yielded abundant results.

<sup>1</sup> Hanes, *Proc. Roy. Soc.*, 1940, [B], 128, 421; *ibid.*, 129, 174; Bourne and Peat, *J.C.S.*, 1945, 877.

## D.—GLYCOGEN

## 1. General

In the animal body, glycogen plays the part of a reserve material, and its physiological importance has led to much research. On the chemical side, its composition is known to be representable by  $(C_6H_{10}O_5)_n$ ; and on hydrolysis it yields maltose in certain conditions and glucose when the hydrolysis is a complete one. It gives a purple-red colour with iodine, and does not reduce Fehling's solution. It is a white amorphous substance, which goes into colloidal solution when shaken with cold water. Glycogen is evidently closely related to starch, and the relationship becomes more obvious when the degradation products of the methylated substances are compared.

## 2. The Constitution and Molecular Size of Glycogen

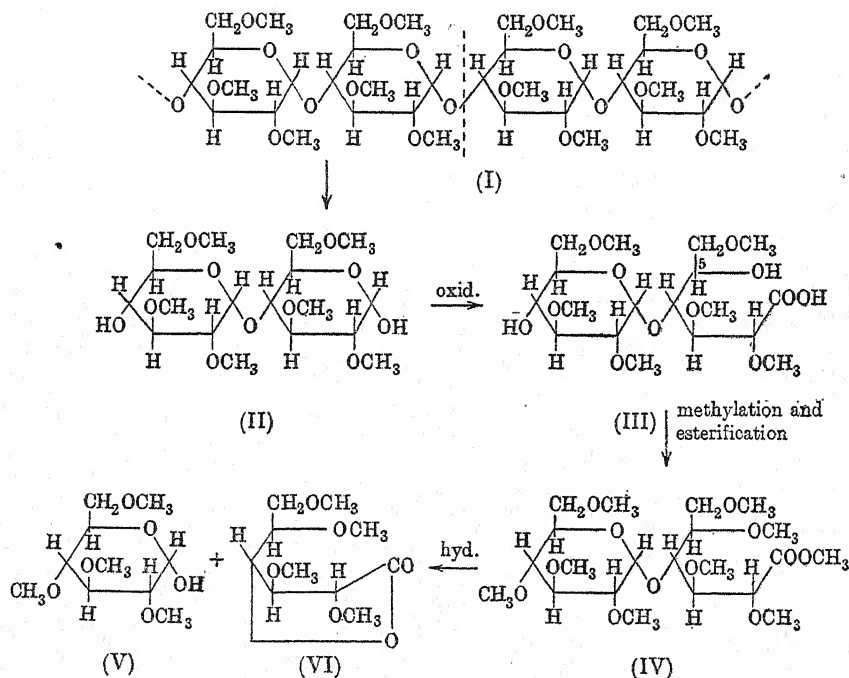
At an early stage in the chemical investigation of glycogen the view was expressed that starch and glycogen were fundamentally identical.<sup>1</sup> When glycogen is acetylated with acetic anhydride in the presence of chlorine or sulphur dioxide as catalyst, glycogen triacetate is obtained in almost quantitative yield. The triacetate can be quantitatively converted into methyl glucoside by the agency of methyl-alcoholic hydrogen chloride. This demonstrates that the polysaccharide contains only glucose units; and further insight is obtained into the molecular structure from the fact that enzyme action transforms glycogen into maltose. When glycogen triacetate in acetone solution is simultaneously deacetylated and methylated by repeated treatment with methyl sulphate and potassium hydroxide, the trimethyl glycogen obtained is indistinguishable in properties from trimethyl starch obtained by similar methods.<sup>2</sup>

Hydrolysis of trimethyl glycogen leads to the isolation of dimethyl glucose, 2:3:6-trimethyl glucose and 2:3:4:6-tetramethyl glucose. Provisionally then, the opinion may be

<sup>1</sup> Karrer, *Helv. Chim. Acta*, 1921, 4, 994; Macbeth and Mackay, *J.*, 1924, 125, 1513.

<sup>2</sup> Haworth, Hirst, and Webb, *J.*, 1929, 2479.

held that glycogen is built up of chains of  $\alpha$ -glucose units. When trimethyl glycogen (I.) is broken down by the action of acetyl bromide in solution in chloroform, derivatives of mono-, di- and trisaccharides are formed. The disaccharide derivative, which was presumably the bromide and monoacetyl derivative of a hexamethyl biose (II.), after the elimination of bromine was oxidized to a bionic acid (III.) This acid was further methylated and esterified to (IV.), and then hydrolysed to 2:3:4:6-tetramethyl glucose (V.), and 2:3:5:6-tetramethyl- $\gamma$ -gluconolactone (VI.).

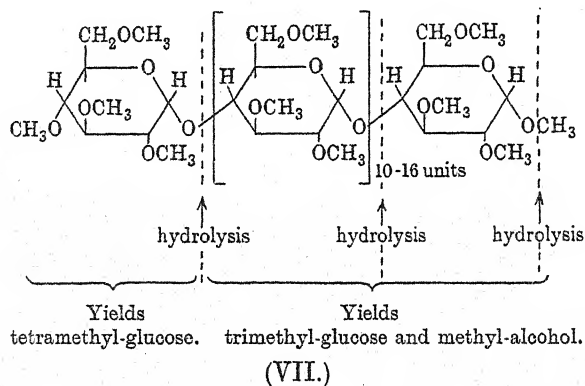


Since 2:3:5:6-tetramethyl  $\gamma$ -gluconolactone (VI.) is produced from the free acid on hydrolysis of the ester (IV.), the 4-position must be involved in the union of this unit with tetramethyl glucose (V.) in the octamethyl bionic ester (IV.). Further, there is no doubt that the 5-position was liberated as a hydroxyl group (see III.) by oxidation of the biose derivative (II.), as direct hydrolysis of the biose derivative (II.) yields only 2:3:6-



trimethyl glucose. Glycogen, therefore, is constituted on the same general plan as starch and consists mainly of  $\alpha$ -glucose units joined together through the 1- and 4-positions as shown above for the methylated derivative (I.)

Quantitative examination of the products of hydrolysis of methylated glycogen prepared from glycogen showed the presence of approximately 9 per cent. of 2:3:4:6-tetramethyl glucose. Since tetramethyl glucose is produced only from an end-group of a glucosidal chain (VII.), it follows that the number of glucose units in methylated glycogen is approximately twelve.<sup>1</sup> By this method of analysis, glycogen from rabbit liver has been shown to have a chain length of eighteen glucose units.<sup>2</sup>



Glycogen which has been exhaustively methylated yields an amount of dimethyl glucose approximately equal to the tetramethyl glucose isolated by hydrolysis.<sup>1</sup> A considerable proportion of this dimethyl glucose is the 2:3-derivative. To explain the di-methylation of certain glucose units of the glycogen molecular chain, it has been suggested that the 1-4 linked  $\alpha$ -glucose chains are themselves joined by a type of union, which links the reducing end of one chain with an hydroxyl of a non-terminal unit in an adjoining chain.<sup>3</sup> Such a unit would, therefore, be united at three points of its ring with adjoining glucose members, leaving only two exposed hydroxyl groups and

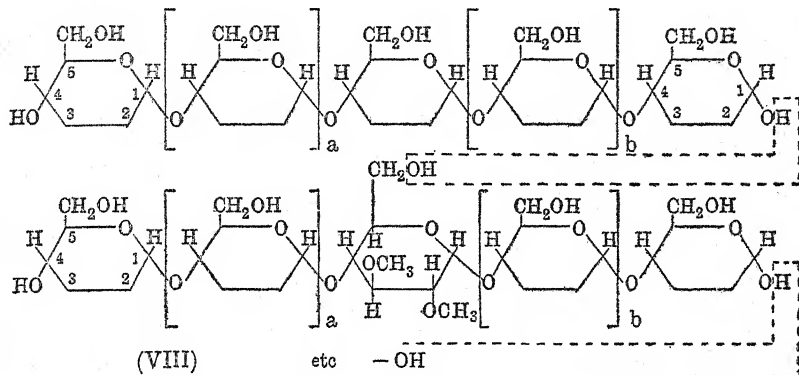
<sup>1</sup> Haworth and Percival, *J.*, 1932, 2277; Bell, *Biochem. J.*, 1935, 2031.

<sup>2</sup> Haworth, Hirst, and Isherwood, *J.*, 1937, 577.

<sup>3</sup> Haworth, Hirst, and Isherwood, *loc. cit.*



ultimately appearing as dimethyl glucose amongst the products of degradation. This glycogen complex may be illustrated as follows (VIII.) :—

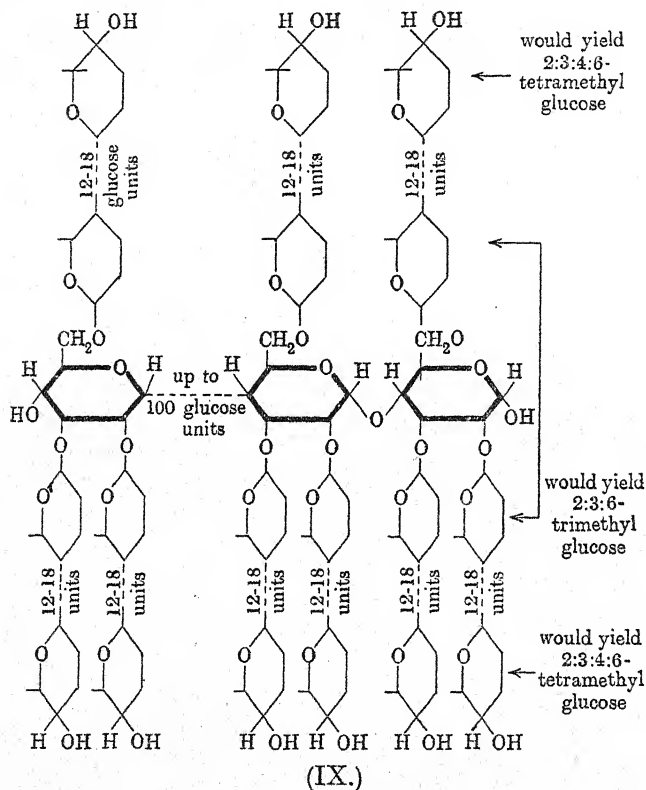


The chemical information at present available does not permit the unit of attachment of the reducing group in the adjacent chain to be specified, nor can it throw any light on the type of bond. Physical evidence favours an individual macromolecular structure for glycogen rather than a micelle-colloidal grouping. Glycogen in such solvents as water, formamide, calcium chloride and formamide obeys van't Hoff's law of osmosis, and consequently it is considered unlikely that the particle is a micelle-colloid. It is concluded that in these solvents the particle size is about 1,750 glucose units, and a molecule composed of 5,000 units is said to exist under certain conditions in formamide solution.

Triacetates of glycogen have been prepared, and their viscosities and osmotic pressures compared with the corresponding measurements of the recovered glycogens. From these and other observations it is concluded that the glycogen molecule in colloidal solution is spherical in shape. The molecule (IX.) is represented as consisting of a central chain, varying in length from 30 to 100 glucose units, bound glucosidally at the positions 1 and 4, carrying side-chains of 12 to 18 glucose units in length. Each central chain unit supports a side chain at position 2, 3 and 6. The length of the central chain varies according to the treatment of the material.<sup>1</sup>

<sup>1</sup> Staudinger and Husemann, *Annalen*, 1937, 530, 1.

According to this theory of the structure of the glycogen molecule, the central chain making up 1.8 to 2.7 per cent. of the whole, would be almost entirely incapable of methylation and should appear unmethylated in the degradation products. The molecule as it stands does not account for the presence of dimethyl glucose and tetramethyl glucose in approximately the



same amounts in the products of degradation of methylated glycogen. The elimination of two side chains from each central chain unit prior to methylation could not account for the amounts of dimethyl glucose isolated, so that some modification of this structure is necessary to make it fit the known facts. Further experimental work on both the chemical and physical sides will doubtless permit a more definite outline of the glycogen molecule to be drawn.

## E.—LAMINARIN

## 1. General

Laminarin occurs plentifully in the fronds of marine algae, during the autumn months, and it has been isolated from *Laminaria cloustoni*, *L. digitata*, *L. saccharina* and *Saccorhiza bulbosa*. This substance yields glucose on hydrolysis, and was the first polysaccharide of the glucose group discovered to have the glucose residues linked together at the 1-3 positions. Laminarin was isolated from *L. digitata* fronds by allowing the dried and finely divided material to stand for some days in dilute hydrochloric acid. Laminarin spontaneously deposited from this solution. The crude material was purified by repeated precipitation from water, followed by washes with alcohol and ether.<sup>1</sup> Hydrolysis of the pure substance with hydrochloric acid gave a yield of 98.5 per cent. glucose.

## 2. The Structure of Laminarin

The triacetate of laminarin on simultaneous deacetylation and methylation gave a quantitative yield of trimethyl laminarin, which on hydrolysis broke down to 2:4:6-trimethyl glucose. When the specific rotations of laminarin and its acetyl and methyl derivatives were compared with the corresponding rotations of the celluloses, lichenins, starches and glycogens. The small negative rotations of laminarin and trimethyl laminarin and the greater negative rotation of the acetyl derivative like the corresponding rotations of cellulose and lichenin and their derivatives suggest that the laminarin molecule is built up of  $\beta$ -glucose units. The specific rotations of the polysaccharides mentioned are given on p. 106 for comparison.

The disaccharide, named laminaribiose (II.), corresponding to maltose from starch and cellobiose from cellulose, has been isolated from the products of catalytic hydrolysis of laminarin. The enzymatic hydrolysis of laminarin to glucose by snail juice is very rapid, but it was possible in the course of the hydrolysis to isolate laminaribiose in the form of its osazone from the reaction mixture.<sup>2</sup> When the hydrolysis of laminarin was

<sup>1</sup> Barry, *Sci. Proc. Roy. Dublin Soc.*, 1938, 21, 615.

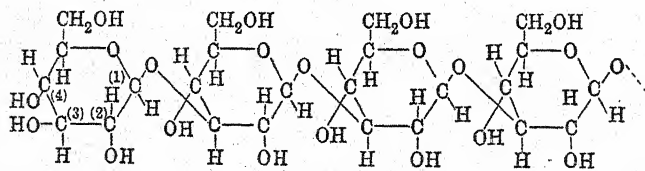
<sup>2</sup> Barry, *ibid.*, 1939, 22, 59; 1941, 22, 423.

	Cellulose	Lichenin	Starch	Glycogen	Laminarin
Polysaccharide .	- 3.45° *	+ 8.3° † - 2.35° *	+ 190°	+ 192°	- 7° to - 16°
Acetyl derivative (chloroform) .	- 22°	- 38.5°	+ 170°	+ 163°	- 52°
Methyl derivative (chloroform) .	- 10°	—	+ 208°	+ 208°	- 4.39°

\*  $[\alpha]_{435.8}^{32^{\circ}}$  In cuprammonium.

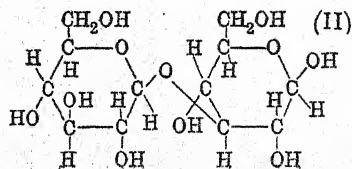
† In 2N-NaOH.

effected by cold concentrated hydrochloric acid or by hot dilute acid, the course of the change could be followed by using the polarimeter. By interrupting the reaction at a suitable stage, it was possible to prepare laminaribiose osazone from the products of hydrolysis. Laminaribiose itself was isolated by using normal oxalic acid as the hydrolysing agent. The reaction was allowed to proceed until it was about two-thirds complete to reduce, as far as possible, the proportion of oligosaccharides present in the liquid. After neutralization with chalk the liquid was fermented by yeast to destroy any glucose present. The solid residue obtained by evaporation of the liquid was dissolved in methyl alcohol, and the laminaribiose separated from higher saccharides by fractional precipitation from solution. Laminaribiose is rapidly converted into glucose by emulsin, a further proof of the presence of the  $\beta$ -glucoside linkage in the polysaccharide. Formulating the  $\beta$ -glucose units as shown below, the laminarin structure may, according to the evidence, be written as (I.), and the biose as (II.).



(a)

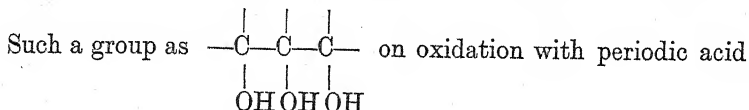
(I)



(II)

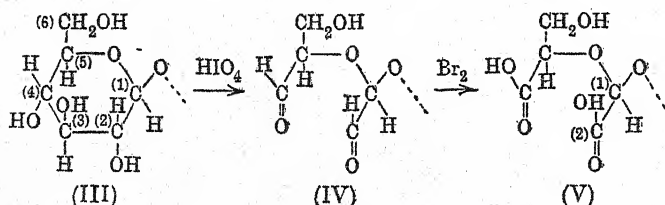
3. *The Molecular Size of Laminarin*

The length of the laminarin molecular chain was estimated by an ingenious adaptation of the periodic acid oxidation method for the examination of polysaccharides. Periodic acid reacts with a carbon chain containing adjacent hydroxyl groups giving rise to aldehyde groups by fission of a carbon-carbon bond.



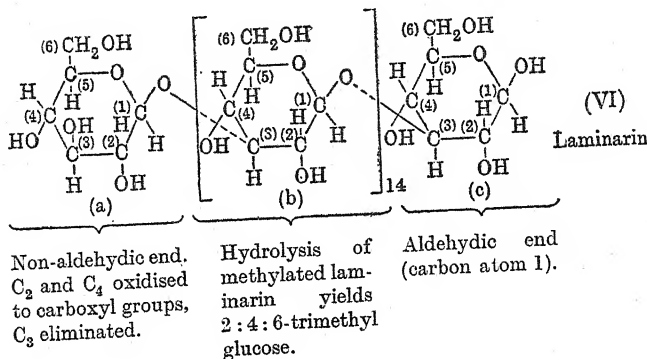
loses the central carbon atom and yields two aldehyde groups. When laminarin was treated with periodic acid a small but definite amount of oxidation occurred. Inspection of structure (I.) will show that the only part of the laminarin molecule containing adjacent hydroxyl groups of a non-aldehydic nature is in the end glucose unit marked (a) at carbon atoms (2), (3), and (4). The two aldehyde groups formed by the action of periodic acid may be further oxidized by bromine to carboxyl groups. At the same time the bromine appears to oxidize the terminal aldehyde units of the molecule, but allowance can be made for this small additional carboxyl content in calculating the percentage of dicarboxylated end-group in the modified laminarin. The acidity of the molecule may now be estimated either by direct neutralization or by the formation of the silver salt. From the results of this method of determining the size of the molecular chain it was concluded that the laminarin molecule contained sixteen glucose units.<sup>1</sup>

The changes of laminarin on oxidation with periodic acid and bromine are shown in structures (III.), (IV.), and (V.).



<sup>1</sup> Barry, Dillon, and McGettrick, *J.*, 1942, 183; Barry, *ibid.*, 578.

The structure (IV.) was confirmed by the detection of glyoxylic acid (from carbon atoms 1 and 2) among the products of its hydrolysis. Laminarin may now be formulated as (VI.) :—



A polysaccharide obtained from baker's yeast also yields 2 : 4 : 6-trimethyl glucose after methylation and hydrolysis.<sup>1</sup>

Agar-agar, the gelatinous extract of certain East Indian seaweeds, has the 1-3 glycoside linkage in its molecule, as the chief product of the hydrolysis of the methylated agar is 2 : 4 : 6-trimethyl-*D*-galactose.<sup>2</sup>

The 1-4 and 1-3 linkages are not, however, the only glycoside bonds found in the polysaccharide molecules. The 1-6 glycoside linkage has been detected in the dextran produced from sucrose by organisms of the *Leuconostoc* species,<sup>3</sup> and in the water soluble glucosan from barley roots.<sup>4</sup>

## F.—CONCLUSION

The foregoing account, lengthy as it is, does not pretend to include all the researches on members of the polysaccharide class which have been carried out during the last ten or fifteen years. Had any effort at completeness been made, the material would have filled a volume instead of a chapter. Since selection of some sort was rendered inevitable by the limitation of available

<sup>1</sup> Hassid, Joslyn, and McCready, *J. Amer. Chem. Soc.*, 1941, **63**, 295.

<sup>2</sup> Percival and Somerville, *J.*, 1937, 1615.

<sup>3</sup> Peat, Schlüchterer and Stacey, *J.*, 1939, 581 ; Daker and Stacey, *J.*, 585.

<sup>4</sup> Hassid, *J. Amer. Chem. Soc.*, 1939, **61**, 1223.

space, it seemed best to pick out from the mass of data those parts which have the greatest theoretical interest and which have the further quality of lending themselves to a logical treatment. As the preceding sections show, this work on the polysaccharides exhibits in a vivid manner how even the most intricate structural problems can be approached with success. In carbohydrate research the reader can recognize the various stages through which the investigations have passed. First came the initial idea of fixing the labile structures of the carbohydrates by means of methylation, and close on this followed the devising of experimental methods of putting the idea into practice. In the next stage, numbers of definite methylated sugars were prepared which were to serve as comparison compounds in the identification of the fission-products of the methylated carbohydrates of complex constitution. This stage was the longest and most difficult, since it represents an enormous amount of detailed work in the case of each sugar examined. At the end of it, all was ready for a great advance; and in the final stage, the most striking feature is the rapidity with which intricate problem after intricate problem is finding its solution.



## CHAPTER IV

### PECTIC SUBSTANCES AND ALGINIC ACID

#### A.—PECTIC SUBSTANCES

##### 1. *Introductory*

PECTINS are substances of high molecular weight closely related to the polysaccharides. They are widely distributed in plant tissues, especially in fruits, fleshy roots, and vegetables. They are one of the accompaniments of cellulose in the cell-walls of plants and occur as calcium salts in the middle lamella of tissues, where they appear to act as binding agents, holding adjacent cells together. Various pectin compounds have from time to time been isolated and described. The characteristics of three principal types are summarized in Table I.

TABLE I.

Pectose (Protopectin)	An insoluble pectin-cellulose complex of the cell-walls of plant tissues. It is the pectin precursor in unripe material, and changes gradually, as the plant matures, into simpler pectin substances.
Pectins . . . .	Gelatinous substances showing the properties of typical emulsoids, and capable, with suitable amounts of sugar water and acid, of forming jellies. They are esters of polygalacturonic acids.
Pectic Acids . . . .	Partly or wholly hydrolysed pectins. They occur in over-ripe fruit and do not form jellies.

In recent years there has been a great increase in the scientific investigation of plant products of economic importance with a corresponding increase in the study of the pectin substances of fresh and stored fruits, vegetables, and their manufactured

products, textile fibres, and the natural raw materials of the wine, beer, cider, wood pulp, sugar beet, and starch industries. Pectin substances may be obtained on the large scale from such materials as apple pomace and orange or lemon pulp, by extraction with warm acid solutions followed by precipitation by means of alcohol or aluminium hydroxide. Pectin in colloidal solution carries a negative charge and mutual precipitation occurs when positively charged aluminium hydroxide is formed in the solution from ammonia and aluminium sulphate. The hydroxide is removed from the crude pectin by conversion into the chloride, which dissolves in alcohol. On the laboratory scale, "soluble" pectin can be conveniently obtained by treating the plant tissues with warm solution of a salt capable of removing calcium from solution. Ammonium oxalate is very suitable for this purpose.

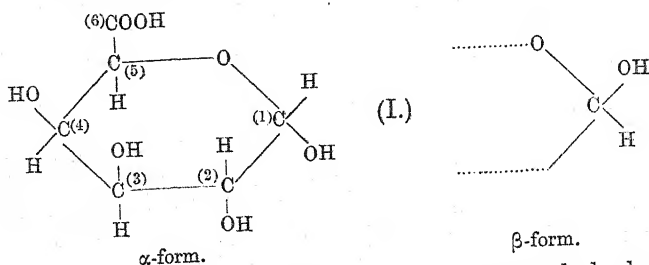
## 2. The Constitution of Pectose (Protopectin)

Owing to the insolubility of pectose in ordinary solvents and its sensitiveness and variable behaviour towards acids and alkalis, its isolation in an unaltered form has proved impossible. The best method, so far devised, is the successive use of water to remove "soluble" pectin, alcohol and ether to take up oil and resins, and cuprammonium hydroxide solution (Schweitzer's reagent) to dissolve uncombined cellulose. Further treatment with dilute acetic acid removes any traces of copper left.<sup>1</sup> Pectose obtained in this way can be converted into pectin and cellulose by hydrolysis. There are, however, variations in the properties of pectose obtained from different sources, especially in its behaviour towards hydrolysing agents. The variations are ascribed to differences in composition of the pectin-cellulose complex; the greater the cellulose content of the complex the greater is the insolubility of the material, and the greater the resistance to hydrolysis.<sup>2</sup> Pectose like pectin yields *d*-galacturonic acid (I.) in quantity on hydrolysis, and this compound is regarded as the foundation unit of both substances.<sup>3</sup>

<sup>1</sup> Sucharipa, *J. Amer. Chem. Soc.*, 1924, 46, 145.

<sup>2</sup> Carré, *Biochem. J.*, 1925, 19, 257.

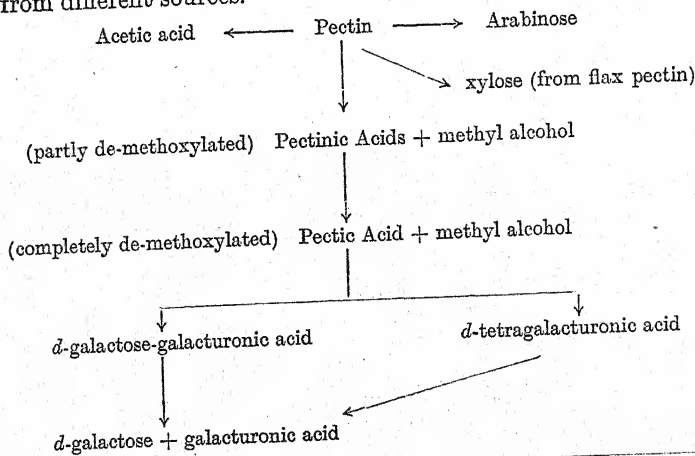
<sup>3</sup> Ehrlich, *Chem. Ztg.*, 1917, 41, 197; *J. Soc. Chem. Ind.*, 1917, 36, 502.



Pectose and pectin substances also yield methyl alcohol, arabinose, galactose and pectic acid on hydrolysis, and from the evidence available it is concluded that pectose is the parent substance of pectin. Pectose is not one single substance but varies in composition with one to eight cellulose groups in a glycosidic structure.<sup>1</sup>

### 3. The Constitutions of Pectin and Pectic Acid

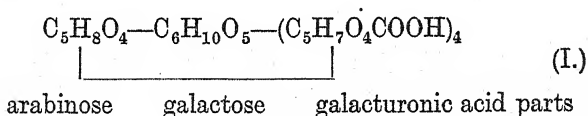
Pectin may be obtained from fruit juices or from the hot water extract of roots such as beets and carrots by precipitation with alcohol, and from pectose by limited acidic or enzymatic hydrolysis. The product obtained is a mixture of pectin and pectinic acids, the compositions of which vary with the raw material used and the method of isolation. The diagram indicates the compounds which have been isolated from pectins from different sources.



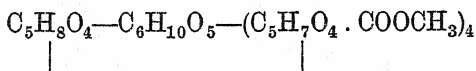
<sup>1</sup> Carré, *loc. cit.*

Pectins from different sources appear to vary in composition ; sugar-beet pectin yields galacturonic acid, galactose, arabinose, methyl alcohol and acetic acid, whilst flax pectin yields xylose in addition. Very little is known of the mode of linkage of galactose and arabinose in the pectin molecule, and indeed it is argued from some experimental results that they are not essential constituents of the pectin skeleton.<sup>1</sup> Pectin is considered to be a methyl ester of a polygalacturonic acid, and yields a series of pectinic acids of decreasing methoxy content and increasing acidity when it is hydrolysed with acids of increasing strengths. With alkali, pectin is converted into pectic acid and methyl alcohol.

From time to time structures have been suggested for pectic acid.<sup>2</sup> From analyses of calcium pectate the molecular formula  $C_{35}H_{50}O_{33}$  was assigned to pectic acid, and from the results of quantitative hydrolysis of the acid it was concluded that the molecule was composed of four units of galacturonic acid along with one each of galactose and arabinose.<sup>3</sup> A ring structure was given to pectic acid (I.).



On this basis pectin would be the tetramethoxy derivative (II.),



and the pectinic acids, the mono-, di-, and tri-methoxy-pectic acids.

Modifications of this structure have been proposed. Pectic acid from sugar beet and flax yields tetragalacturonic acids, and consequently the basic structure has been formulated as a ring of four galacturonic acid units ; and as arabinose and galactose in varying proportions have also been isolated, an arabinogalactose disaccharide unit was considered to be attached

<sup>1</sup> Schneider and Fritsch, *Ber.*, 1937, 70, [B], 1611.

<sup>2</sup> Schryver and Haynes, *Biochem. J.*, 1916, 10, 539 ; Fellenberg, *Biochem. Z.*, 1918, 85, 45, 118 ; Ehrlich, *Chem. Ztg.*, 1917, 41, 197 ; *J. Soc. Chem. Ind.*, 1917, 36, 502.

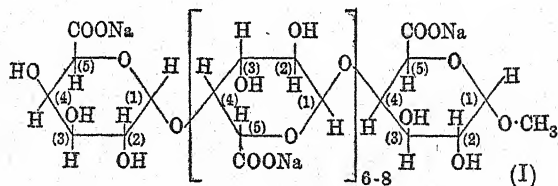
<sup>3</sup> Nanji, Paton and Ling, *J. Soc. Chem. Ind.*, 1925, 44, 253.

through a galacturonic acid hydroxyl as a side chain.<sup>1</sup> A larger molecule containing eight galacturonic acid groups in the form of two closed rings has also been suggested.<sup>2</sup> The results of further and more recent work favour an open chain type of molecule of higher molecular weight than those just described.

A compound has been isolated from citrus pectin by mild acid extraction followed by neutralization with calcium hydroxide. The salt was decomposed by acid and the resulting polygalacturonide (pectic acid) washed and dried. Obtained in this way the polygalacturonide was very pure, free from galactose and arabinose, and yielded 95-99 per cent. of galacturonic acid on hydrolysis.

The polygalacturonide was refluxed with dry methyl alcohol-hydrogen chloride solution and the insoluble glycoside-methyl-ester isolated, purified and analysed. The results of ultimate analyses agreed closely with those required for a compound containing eight to ten galacturonic acid units. The glycoside-ester was converted into the sodium salt by the action of sodium hydroxide solution, which completely hydrolyses the ester groups without affecting the glycoside group. The barium salt was obtained through the sodium salt. Analyses of the two salts also indicated that the polygalacturonide was composed of eight to ten units.

Estimations of the glycoside methoxyl and sodium contents agreed very closely with the theoretical requirements of a methyl-glycoside of sodium polygalacturonate of 8-10 units (I.).



The table given on p. 115 summarizes the analytical data.<sup>3</sup>

<sup>1</sup> Ehrlich, *Z. angew. Chem.*, 1927, 40, 1305; Ehrlich and Schubert, *Ber.*, 1929, 62, 1974; Ehrlich, *Cellulosechemie*, 1930, 11, 130; *Biochem. Z.*, 1932, 250, 525; 251, 204.

<sup>2</sup> Myers and Baker, *Delaware Agr. Exp. Sta.*, 1934, Bull. 187.

<sup>3</sup> Morell, Baur, and Link, *J. Biol. Chem.*, 1934, 105, 1.

	1	2		3		4
		<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	
No. of Units.	Polyester-glycoside	Polysodium salt glycoside		Polybarium salt glycoside		Polyacid-glycoside
	% O. CH <sub>3</sub>	% O. CH <sub>3</sub>	% Na	% O. CH <sub>3</sub>	% Ba	% O. CH <sub>3</sub>
8 calculated	18.00	1.92	11.39	1.56	27.71	2.15
9 „	17.82	1.71	11.41	1.37	27.80	1.92
10 „	17.67	1.54	11.43	1.25	27.85	1.73
Values found	18.00	1.40	11.39	1.30	26.8	2.18

It will be observed from the table that the scheme of analysis included estimations of methoxyl from ester and glycoside groups (col. 1), and of methoxyl from glycoside alone (cols. 2 *a*, 3 *a* and 4). These figures of methoxyl determinations show the ratio between the terminal unit and the rest of the molecule, and on the assumption that the molecule has a straight chain structure, the determination of the glycoside methoxyl is a measure of the molecular chain length, comparable with the other end-group methods of analysis which have been employed with success in investigations of the structures of cellulose and starch.

These conclusions as to the size of the pectic molecules are supported by viscosity measurements,<sup>1</sup> and the chain formation is probable as X-ray examinations show that pectin derivatives have thread-like molecules.<sup>2</sup>

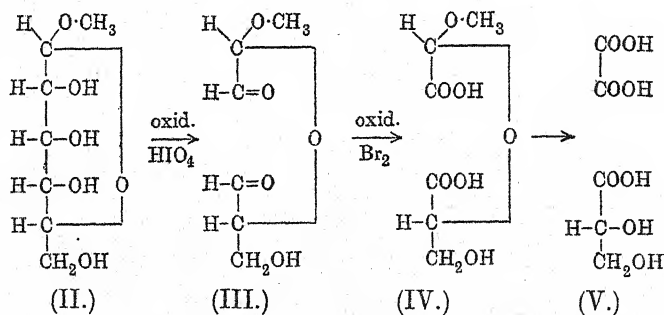
The skeleton of the pectin substances may be regarded as a chain of galacturonic acid units with varying proportions of free carboxyl and methyl ester groups present. From acidity measurements it appears unlikely that any of the carboxyl groups have been transformed into lactone groups.<sup>3</sup> The evidence referring to galactose, and arabinose is conflicting. On the one hand a considerable body of experimental facts points to both compounds forming part of the molecule, though in no fixed proportions. On the other hand it is contended that

<sup>1</sup> Henglein and Schneider, *Ber.*, 1936, 69, 309.

<sup>2</sup> Morell, Baur, and Link, *loc. cit.*; Schneider and Fritsch, *Ber.*, 1936, 69, 2530, 2537.

<sup>3</sup> Schneider and Fritsch, *loc. cit.*

they (and similarly, acetyl groups) occupy no primary place in the molecular structure.<sup>1</sup> Inspection of the structure given for the methyl glycoside of sodium polygalacturonate (I.) shows that the mode of linkage between the different galacturonic units is formulated as the 1:4- $\alpha$ -glycoside type. The  $\beta$ -linkage has also been suggested.<sup>2</sup> Further work, however, is necessary before either can be finally accepted. We are on firmer ground when we examine the evidence for the 1:4-linkage of the galacturonic acid units in the chain formation. Periodic acid is employed to oxidize the carbon chains of polyhydroxy compounds,<sup>3</sup> and acts only in the presence of two adjacent hydroxyl groups.<sup>4</sup> Treated in this way with periodic acid, methylglycosides (II.) are attacked between carbon atoms 2 and 3, giving rise to dialdehyde-acetals of the type shown (III.) by loss of carbon atom 3.\* Further oxidation using bromine converts a dialdehyde-acetal into a dicarboxylic acid (IV.), which can be isolated in the form of the strontium or barium salt and identified. The proof of the structure of such an acid, and particularly the proof of the presence of a *d*-glyceric acid (V.) moiety in the molecule, limits the glycoside ring to the pyranoside (1, 5) or septanoside (1, 6) structure.<sup>5</sup> Other well-known evidence, however, excludes the 1, 6-ring. The following scheme shows the steps in the changes:—



<sup>1</sup> Schneider and Fritshi, *loc. cit.*

<sup>2</sup> Frey-Wyssling, *Protoplasma*, 1936, 25, 262.

<sup>3</sup> Malaprada, *Bull. Soc. Chim.*, 1928, 43, 683; 1934, 1, 833.

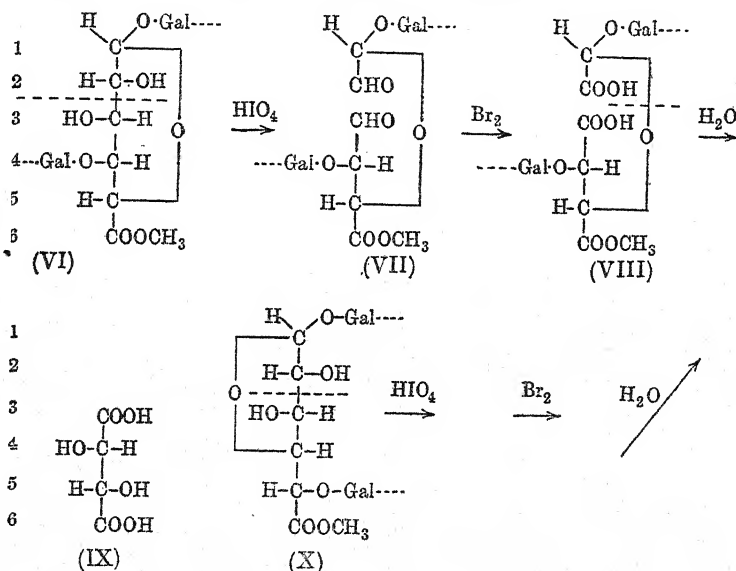
<sup>4</sup> Fleury and Lange, *Compt. rend.*, 1932, 195, 1395; *J. Pharm. Chim.*, 1933, 17, 196; Karrer and Pfäehler, *Helv. Chim. Acta*, 1934, 17, 766.

<sup>5</sup> Jackson and Hudson, *J. Amer. Chem. Soc.*, 1936, 58, 378; 1937, 59, 994.

\* Starch, cellulose and other polysaccharides are attacked in the same way, but without the elimination of carbon atom 3.



These experimental methods and lines of reasoning have been adopted in an investigation of the more complex molecular formation of methyl-polygalacturonate (VI.) prepared from natural pectin. When this ester was oxidized with periodic acid and bromine in succession, and the glycoside bonds hydrolysed with acid, potassium acid tartrate (IX.) was finally isolated from the reaction mixture.<sup>1</sup> It follows that the linkages between the galacturonate residues must be either 1:4-pyranoside (VI.) or 1:5-furanoside (X.). The following scheme summarizes the steps in the possible changes.



Galacturonic acid itself has been shown to contain the same ring structure (pyranose) as galactose, and it may be considered provisionally that this formation persists in the polygalacturonates.<sup>2</sup>

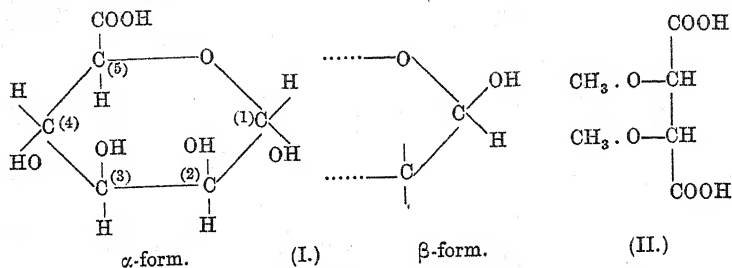
## B.—ALGINIC ACID

Alginic acid is closely related to pectic acid in its physical and chemical properties. It is obtained as a very gelatinous precipitate from certain seaweeds by treating the sodium car-

<sup>1</sup> Levene and Kreider, *J. Biol. Chem.*, 1937, 120, 591.

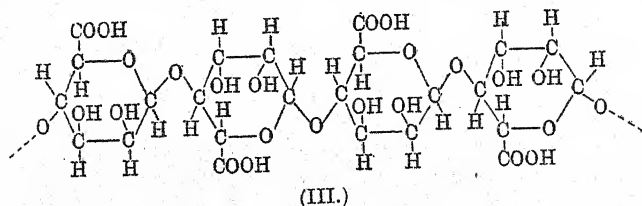
<sup>2</sup> Liemann and Link, *J. Biol. Chem.*, 1934, 104, 195.

bonate extract with dilute hydrochloric acid. Methyl alcoholic hydrogen chloride degrades alginic acid to an alginic acid of lower molecular weight and *d*-mannuronic acid (I.). The simpler alginic acid on methylation followed by hydrolysis yielded 2:3-dimethyl *d*-mannuronic acid, and simultaneous hydrolysis and oxidation with nitric acid gave *i*-dimethoxy-succinic acid (II.).



The major portion of the alginic acid molecule is therefore composed of a chain of *d*-mannuronic acid units. As positions 2 and 3 of the units can be methylated, and in view of the stability and large negative optical rotation of alginic acid, the molecular chain probably has 1-4 glycoside linkages.

It is concluded that at least 50 per cent. of the alginic acid molecule is composed of  $\beta$ -*d*-mannuronic acid units joined by 1-4 linkages. This is represented in structure (III.).



In concluding this chapter attention may be drawn to the remarkable similarity in the molecular structures of substances so different as cellulose, laminarin, glycogen, starch, pectic acid, and alginic acid. The glycoside union is common to all and each contains, with the possible exception of starch, one type of monosaccharide unit only.

## CHAPTER V

### THE SESQUITERPENE GROUP OF COMPOUNDS

#### A. INTRODUCTORY

THE compounds known as terpenes are usually, for convenience, divided into three classes: the hemiterpenes with the formula  $C_5H_8$ ; the true terpenes, which are reduced benzene derivatives, with the composition  $C_{10}H_{16}$ ; and the sesquiterpenes having the general formula  $C_{15}H_{24}$ . The hemiterpenes do not occur in nature; but the most characteristic member of the class, isoprene, is obtained by the distillation of rubber, so that evidently the  $C_5H_8$  skeleton is to be found among natural products. The true terpenes, with ten carbon atoms in their structure, are widely distributed, occurring as they do in the saps of many plants. With them are associated the sesquiterpenes.

The investigation of the terpene group as a whole has fallen into fairly well-marked chronological stages. The third quarter of the nineteenth century was devoted to clearing up the problems presented by the cyclic terpenes. At the end of the century, interest passed to the group of olefinic terpenes; and considerable progress was made in that field. The sesquiterpenes were taken in hand; and even at the present day our knowledge of the field is scanty; though enough has been done to lay bare the outlines of the subject and to suggest the lines along which future work will probably proceed. More recently the di- and triterpene groups of compounds have yielded to investigation.

The main object of the present chapter is to indicate the inter-relationships of certain among these sesquiterpenes and to describe some of the information which has been gained as to the constitution of these substances.

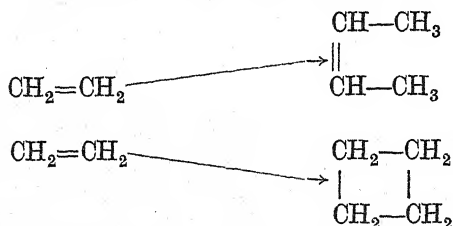
Before entering upon individual problems, however, it seems well to devote a paragraph or two to certain general questions which may serve to simplify the subject.

Inspection of the table below will bring out immediately the simple relationships which the formulæ of the simpler terpenes and of rubber bear to one another :

Hemiterpenes . . . . .	$C_5H_8$	=	$C_5H_8$
Terpenes . . . . .	$C_5H_8 \times 2$	=	$C_{10}H_{16}$
Sesquiterpenes . . . . .	$C_5H_8 \times 3$	=	$C_{15}H_{24}$
Rubber . . . . .	$C_5H_8 \times n$	=	$(C_5H_8)_n$

These figures suggest at once that the whole terpene group is built up on a basis composed of five carbon and eight hydrogen atoms ; and it will be convenient at this point to examine the various stages of saturation which may result from the polymerization of the  $C_5H_8$  unit.

Two molecules, each containing an ethylenic linkage, can be supposed to unite in either of two ways : (1) to form an open chain ; and (2) to yield a cyclic compound.



Now clearly from the above formulæ it is seen that the linking of the two ethylenic molecules in an open chain has resulted in the disappearance of one ethylenic bond ; whilst when a cyclic structure is produced, two ethylenic bonds disappear.

Let this be applied to the case of the sesquiterpenes. In order to link together three of the fundamental  $C_5H_8$  nuclei, two junctions are necessary :  $C_5H_8-C_5H_8-C_5H_8$ . Each of these junctions implies the disappearance of one ethylenic bond, if the new molecule has an open-chain structure. Since each isoprene molecule contains two ethylenic linkages, there are six double bonds present at the start. Two of these are used up in forming the long chain ; which leaves four double bonds present in the final product.

Now the formation of a cyclic structure from this long open chain will demand the disappearance of another double bond ; so that obviously a monocyclic sesquiterpene will have only three ethylenic linkages left in its structure.

Further ring-formation to produce a dicyclic sesquiterpene will entail the elimination of yet another double bond, leaving two ethylenic linkages in the dicyclic sesquiterpene molecule.

By the same reasoning, a tricyclic sesquiterpene must have only a single ethylenic bond and a tetracyclic grouping must be a saturated hydrocarbon.

For the sake of clarity, these facts may be put in the form of a table.

<i>Sesquiterpene Type</i>	<i>Number of Double Bonds</i>
Olefinic . . . . .	4
Monocyclic . . . . .	3
Dicyclic . . . . .	2
Tricyclic . . . . .	1
Tetracyclic . . . . .	0

It may be recalled that the same rules hold good in the group of ordinary terpenes of the composition  $C_{10}H_{16}$ . These may also be regarded as derived from a polymerization of hemiterpenes containing two double bonds; and the same reasoning leads to the conclusion that olefinic terpenes derived from two hemiterpene molecules should contain three double bonds; whilst monocyclic terpenes such as limonene should contain two ethylenic linkages; and dicyclic members of the group like camphene should have only a single ethylenic bond in their structures. This is, of course, exactly what is found in practice.

In distinguishing between members of the sesquiterpene class, the refractivities of the various sesquiterpene structures yield some assistance. The values calculated for the molecular refractivities of the different isomeric forms are:

Open-chain type . . . . .	69.60
Monocyclic type . . . . .	67.87
Dicyclic type . . . . .	66.13
Tricyclic type . . . . .	64.40
Tetracyclic type . . . . .	62.66

These values differ from each other sufficiently to make the refractivity of some help in classifying the various sesquiterpenes, and in suggesting the chemical methods of attack which can best be utilized in determining the constitution of a given substance. An illustration of this will be given in a later section when the constitution of zingiberene is discussed.

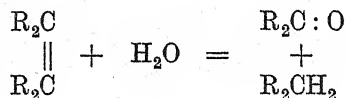
## B.—FARNESOL, NEROLIDOL, AND FARNESENE

Farnesol<sup>1</sup> has the composition  $C_{15}H_{26}O$ . It is found in musk kernels, in the flowers of certain acacias (e.g. *Acacia Farnesiana*) and other plants; and it appears to be the main cause of the odour of lindens.

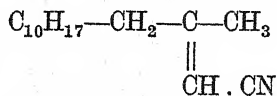
On oxidation, farnesol yields a substance farnesal, which has the composition  $C_{15}H_{24}O$ . Since its reactions prove farnesal to be an aldehyde, it is clear that farnesol is a primary alcohol. When the oxime of farnesal is dehydrated, it yields a nitrile. On hydrolysis, this nitrile yields farnesenic acid and also a ketone with the composition  $C_{13}H_{22}O$ . This ketone has been identified as dihydro-pseudo-ionone:



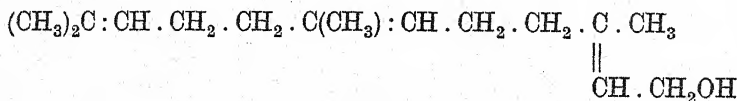
This formation of a ketone by hydrolysis recalls the case of pulegone, which breaks up with the production of methylcyclohexanone and acetone when it is hydrolysed.\* The reaction is evidently an addition of water to a double bond in this fashion:



On this basis, the nitrile mentioned above must have the constitution represented by:



and the primary alcohol farnesol must be:



Farnesol.

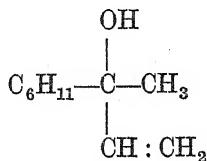
Isomeric with farnesol, there is a second alcohol known as

<sup>1</sup> Haarmann and Reimer, D.R.P. 149603, 150501; Kerschbaum, *Ber.*, 1913, 46, 1732; Harries\* and Haarmann, *ibid.*, 1737; Semmler and others, *Ber.*, 1917, 50, 1836.

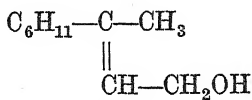
\* See Vol. I., p. 190.

nerolidol<sup>1</sup> (originally named peruvial) which occurs in orange blossom and Peru bark. On treatment with acetic anhydride, nerolidol is rearranged into farnesol, which indicates a close relationship between the two substances. Further, on oxidation, nerolidol yields the same acid, farnesenic acid, which is obtained by the oxidation of farnesol.

This behaviour is an exact parallel to that shown by linalool among the ordinary olefinic terpenes, since it is converted by the action of acetic anhydride into nerol:

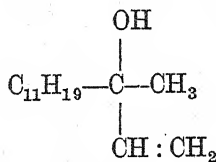


Linalool.

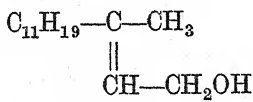


Nerol.

Ruzicka<sup>2</sup> was led by this similarity to suggest that the formulæ of nerolidol and farnesol had analogous endings to their chains so that their formulæ might be written thus:



Nerolidol.



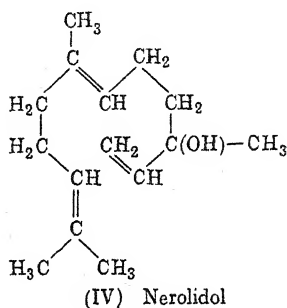
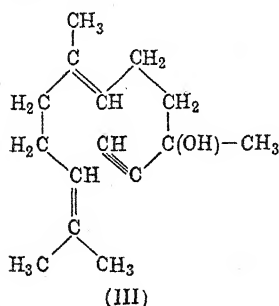
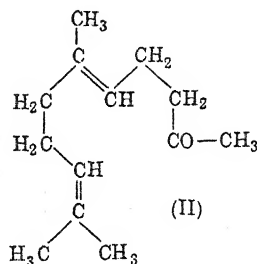
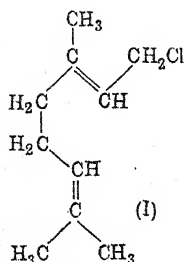
Farnesol.

This view was confirmed by the complete synthesis of nerolidol in the following manner. Geranyl chloride (I.) was treated with acetoacetic ester, yielding the dihydro-pseudo-ionone (II.). Condensation of this with acetylene in presence of sodamide resulted in the formation of dehydronerolidol (III.), which on reduction with sodium in moist ether was converted into nerolidol (IV.). This synthetic nerolidol corresponds exactly with natural nerolidol in chemical properties, though of course it was optically inactive whereas natural nerolidol is dextro-rotatory.

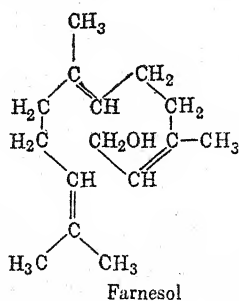
<sup>1</sup> Hesse and Zeitschel, *J. pr. Chem.*, 1902, 66, 503; Thoms, *Arch. Pharm.*, 1897, 237, 271.

<sup>2</sup> Ruzicka, *Helv. Chim. Acta*, 1923, 6, 483.





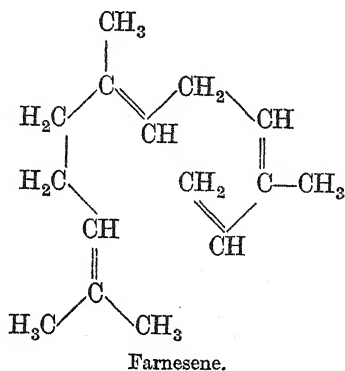
Farnesol is therefore the corresponding analogue of nerol :



It will be borne in mind, of course, that a compound such as farnesol will probably exist as a mixture of geometrical isomers. Inspection of the formula will show that four such isomers are theoretically possible. The formulæ of farnesal and farnesenic acid are got by substituting  $-\text{CHO}$  and  $-\text{COOH}$  for the  $-\text{CH}_2\text{OH}$  group in the above.

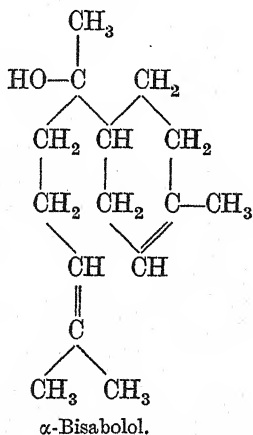
So far, we have been concerned with oxygen derivatives ; but we may now turn to the corresponding terpene, farnesene.

This is obtained, along with farnesol, when nerolidol is treated with acetic anhydride. It seems probable that its structure is this :



#### C.—BISABOLOL AND BISABOLENE<sup>1</sup>

Farnesene, when acted upon for some hours by cold acetic acid in presence of sulphuric acid, gives rise to the acetate of a monocyclic sesquiterpene alcohol. This alcohol is believed to be  $\alpha$ -bisabolol, for which the structure below has been suggested.



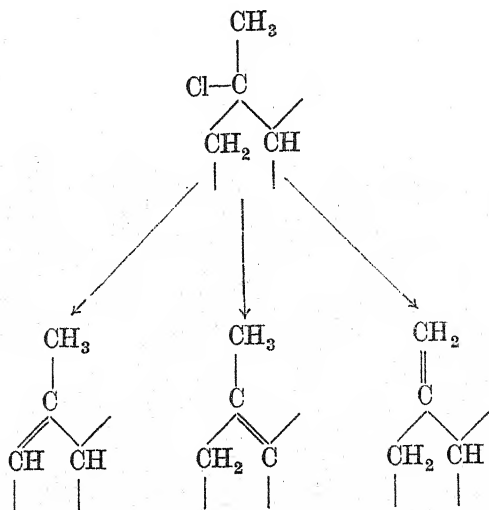
<sup>1</sup> Ruzicka, *Helv. Chim. Acta*, 1923, 6, 483 ; Ruzicka and Capato, *ibid.*, 925, 8, 259.

The alcohol is separable from farnesol by means of phthalic anhydride, which attacks farnesol but leaves bisabolol unaffected.

The same closure of the farnesol open chain to a monocyclic grouping is brought about by means of 90 per cent. formic acid.

The bisabolol obtained by either of these methods can be converted into a trihydrochloride which is identical with the trihydrochloride obtained from natural bisabolene.

When this synthetic trihydrochloride is heated with acetic acid and sodium acetate, it is converted into a monocyclic sesquiterpene which has been shown to be the same as natural bisabolene. The concordance in properties is not absolutely exact between the natural and synthetic products, probably owing to the fact that hydrogen chloride may be eliminated in three different ways from the molecule :

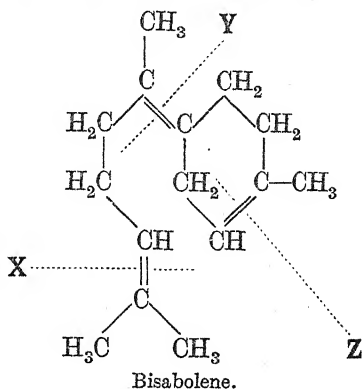


The synthetic bisabolene is thus in all probability a mixture of two or three hydrocarbons which are very difficult to separate ; and hence a slight divergence between its properties and those of the natural material is to be expected. In boiling-point, density, and refractive index, the values are very close in the case of the two compounds.

Ozonization of either synthetic or natural bisabolene yields <sup>1</sup>

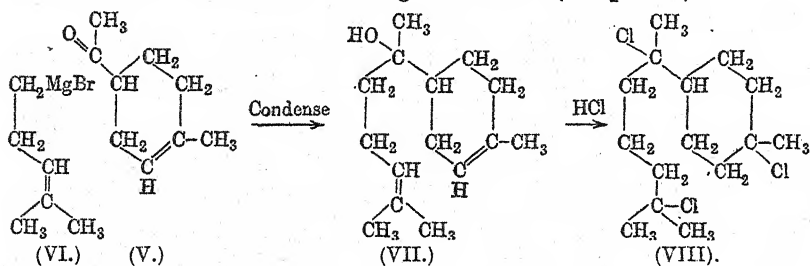
<sup>1</sup> Ruzicka, and Veen, *Annalen*, 1929 468, 133.

acetone, lævulinic acid, and succinic acid. This is easily accounted for, if bisabolene has the following structure.



Rupture of the molecule at **X** yields acetone; and further fission at **Y** and **Z** gives rise to two molecules of lævulinic acid, from which succinic acid can be produced by oxidation.

Bisabolol and the trihydrochloride of bisabolene have been synthesized by a method which does not depend on any rearrangements, and confirms beyond doubt the positions of the double bonds of the alcohol. When 4-acetyl-1-methyl- $\Delta^1$ -cyclohexene (V.) was condensed with the Grignard reagent from 5-bromo-2-methyl- $\Delta^2$ -pentene (VI.), bisabolol (VII.) was formed.<sup>1</sup> The alcohol yielded with hydrochloric acid the trihydrochloride of bisabolene (VIII.), identical with that obtained from nerolidol through farnesene (see p. 125).



#### D.—CADALENE AND EUDALENE

At this point it seems advisable to indicate how the nature of the sesquiterpene skeletons can be ascertained, since a knowledge

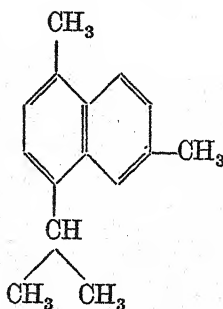
<sup>1</sup> Ruzicka and Liguori, *Helv. Chim. Acta*, 1932, 15, 3.

of the relationships between the various members of the class is thus made simpler.

In 1903, Vesterberg<sup>1</sup> observed that when abietic acid was heated with excess of sulphur to 200° C. and subsequently to 250° C. a small yield of the hydrocarbon retene was obtained. This process evidently is a method of removing hydrogen and so converting a reduced member of the benzene series into its parent. For some reason, this discovery of Vesterberg's does not seem to have attracted the attention it deserved; and it was only after a number of years that it found a wider application.

Ruzicka and Meyer<sup>2</sup> applied Vesterberg's method to the sesquiterpene cadinene, and in this way they obtained a new hydrocarbon, cadalene, which has the formula  $C_{15}H_{18}$ . Since this substance, from its formula, should be highly unsaturated, it was tested with bromine; but it refused to absorb the halogen. This behaviour suggests a benzenoid character; and that idea is strengthened by cadalene forming a picrate. Potassium permanganate oxidizes cadalene readily at ordinary temperatures; and this suggests the elimination of one or more side-chains attached to a benzenoid nucleus, which, from the molecular formula, might be of the naphthalene type.

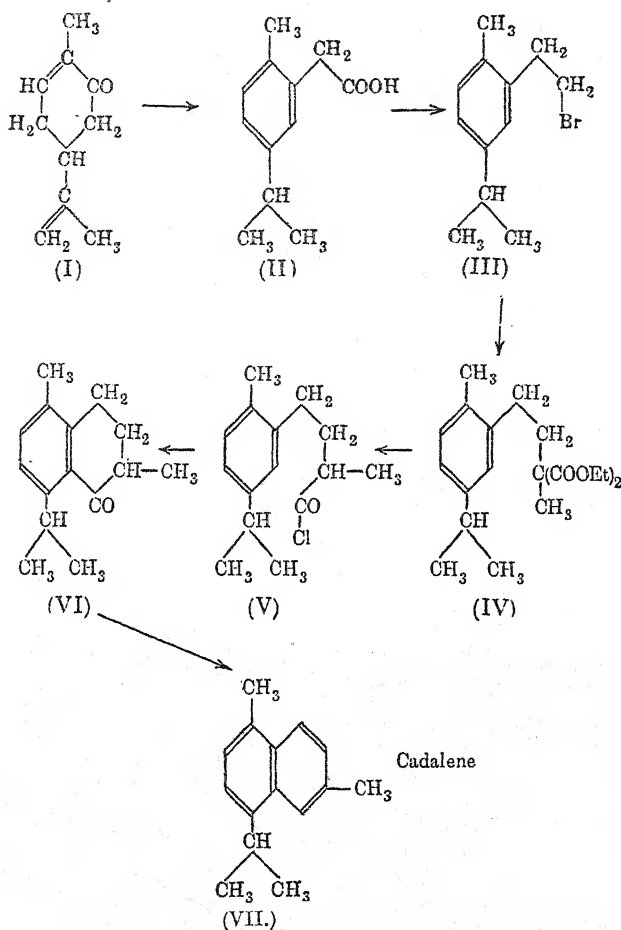
By this time the structure of farnesol was known, and a consideration of its formula led Ruzicka and Seidel<sup>3</sup> to the idea that cadinene might have an analogous constitution and that therefore cadalene might be a naphthalene derivative of the following type:



<sup>1</sup> Vesterberg, *Ber.*, 1903, 36, 4200.

<sup>2</sup> Ruzicka and Meyer, *Helv. Chim. Acta*, 1921, 4, 505.

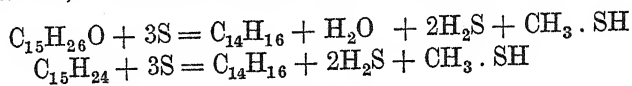
<sup>3</sup> Ruzicka and Seidel, *Helv. Chim. Acta*, 1921, 5, 369.



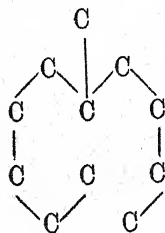
This view they tested by synthesizing this derivative of naphthalene in the following way. Carvone (I.) was converted into 2-cymylacetic ester (II.) by using zinc and bromoacetic ester. The cymylacetic acid, obtained from the ester, was reduced to the corresponding alcohol by Bouveault's method; and the alcohol was then converted into the bromide (III.). This bromide was acted on by methyl-malonic ester, whereby the compound (IV.) was produced. This ester was hydrolysed; carbon dioxide was split off from one carboxyl group; and the chloride (V.) of the resulting acid was prepared. On acting on this with aluminium chloride, an internal Friedel-Crafts reaction occurred, with the

production of the required naphthalene skeleton (VI.). The compound (VI.) was then converted into the corresponding hydrocarbon by reduction with sodium in alcohol, followed by heating with sulphur. The final compound (VII.) proved to be identical with cadalene derived from sesquiterpenes.

This synthesis evidently establishes the structure of the cadinene skeleton beyond dispute. But investigation shows that cadinene is not the base of all the sesquiterpenes. For instance,<sup>1</sup> when the sesquiterpene alcohol eudesmol and the sesquiterpene selinene are dehydrogenated by the Vesterberg method, the reactions take the course shown below :



In each case, it will be noticed, a carbon atom is split off the skeleton of the sesquiterpene derivative; and in both cases the hydrocarbon produced is eudalene and not cadalene. Since eudalene is an aromatic compound, this behaviour suggests that the eliminated carbon atom must lie in a position which would block the conversion of the sesquiterpene into an aromatic ring-compound; so that it has to be eliminated when ring-formation occurs. Now by analogy, it seems reasonable to suppose that the ring-compound formed is a naphthalene derivative; and this implies that the eliminated carbon atom must be attached originally to one of the two carbon atoms common to the two benzene nuclei in the naphthalene structure :

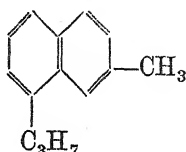
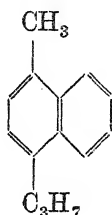


If it were attached anywhere else, it would merely become the nucleus of a normal substituent group; whereas in this particular position it must be removed before cyclization can occur, since these two atoms in the naphthalene structure carry no substituent groups.

<sup>1</sup> Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 345.

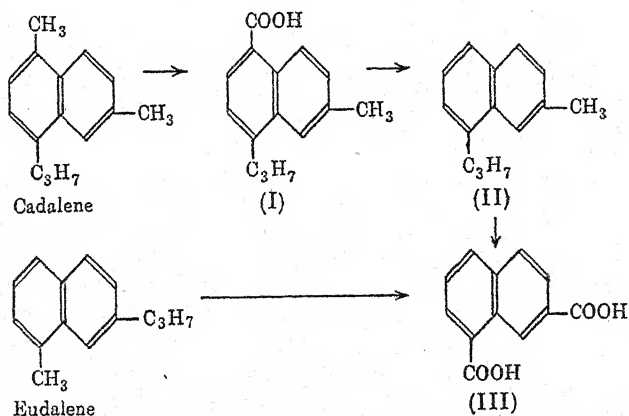


This view of the eudalene structure leaves the remainder of the constitution unsettled; and the next point is to establish the location of the substituents. The first possibility which need be considered is that eudalene is *apo-cadalene*. If so, it must have either of the following structures:



This conception of eudalene's constitution is negated decisively by the fact that Ruzicka and Mingazzini<sup>1</sup> synthesized both these compounds and found them to be different from eudalene.

A fresh hypothesis is suggested by the following evidence. When cadalene is oxidized with chromic acid,<sup>2</sup> it yields a naphthoic acid, which proved to be 6-methyl-4-isopropyl-1-naphthoic acid (I.). On heating this with soda-lime, the carboxyl group is eliminated; and on oxidizing the methyl-isopropyl-naphthalene (II.) thus formed, the product is 1:7-naphthalene dicarboxylic acid (III.). Now the same acid is produced from eudalene



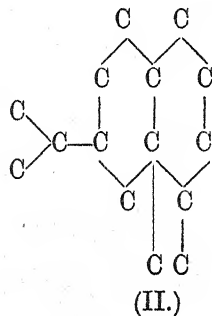
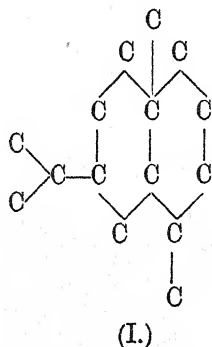
<sup>1</sup> Ruzicka and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 710.

<sup>2</sup> Ruzicka, Meyer, and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 345.

on oxidation. Since eudalene is not *apo*-cadalene, the only possible explanation of these reactions is the one indicated in the formulæ on page 131. Eudalene is therefore a position-isomer of *apo*-cadalene (II.), situations of the methyl and isopropyl groups being exchanged.

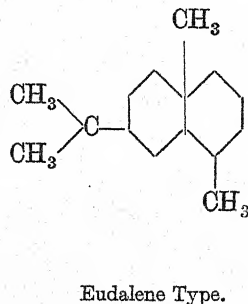
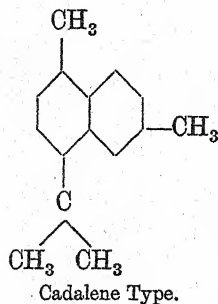
This view has been confirmed by a synthesis of eudalene<sup>1</sup> on the same lines as that already described in the case of cadalene.

Since it has already been shown that the carbon atom eliminated during the formation of eudalene from the sesquiterpenes must be attached to one or other of the central atoms of the naphthalene structure, only two possible sesquiterpene skeletons can be made to agree with the facts :



Since (II.) cannot be derived from three molecules of isoprene owing to the contiguity of the two methyl radicles which it entails, the skeleton (I.) is to be preferred.

It is thus established that two main types of skeleton exist in the sesquiterpene series: the cadalene type and the eudalene type:

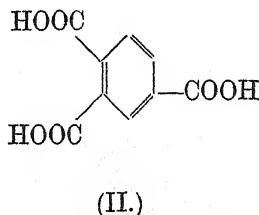
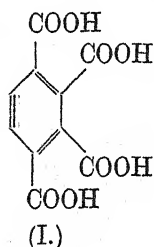


<sup>1</sup> Ruzicka and Stoll, *Helv. Chim. Acta*, 1922, 5, 923.

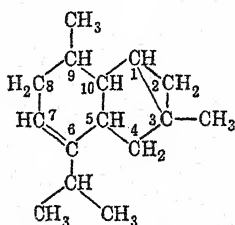


Since the isopropyl group appears in cadalene, it seems probable that it exists also in cadinene; which leads to the inference that both the cadinene double bonds are situated in the cyclic portion of the structure. Now on ozonization, cadinene yields a product which contains all the carbon atoms of cadinene. This disposes of the possibility that both double bonds are in the same ring of the structure, since in this case the carbon atoms between the two double bonds would be eliminated during the decomposition of the ozonide. Further, attempts to reduce cadinene with sodium and amyl alcohol proved unsuccessful, which suggests that the two double bonds do not form a conjugated system.

Oxidation with manganese dioxide and sulphuric acid leads to the production of 1:2:3:4-benzene tetracarboxylic acid (prehnitic acid) (I.) \* and trimellitic acid (II.);



There is a very close relationship between cadinene and the hydrocarbon copaene. When copaene is treated with hydrogen chloride it is converted into cadinene dihydrochloride. Copaene contains only one double bond, and this has been proved to be adjacent to the carbon atom carrying the isopropyl group, at position 6-7.<sup>1</sup>

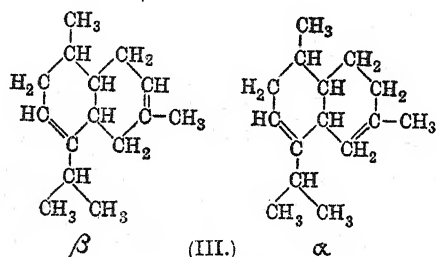


Copaene.

\* Note: This acid has also been referred to as mellophanic acid. See Bamford and Simonsen, *T.*, 1910, 97, 1904, and Smith and Byrkit, *J. Amer. Chem. Soc.*, 1933, 55, 4305.

<sup>1</sup> Semmler and Stenzel, *Ber.*, 1914, 47, 2555.

It may be concluded then, that one of the double bonds of cadinene (III.) is similarly placed. Since the other double bond cannot be in the same ring, and does not form part of a conjugated system, it follows that there are only four possible positions for this double bond in ring II., as position 4-5 is conjugated with position 6-7. Position 1-2 may also be ruled out as a compound of this structure would isomerize under the influence of acid with a shifting of the double bond to position 2-3. Cadinene is not isomerized by warm dilute acid. Of the three remaining possible positions for the second double bond the two adjacent to the carbon atom carrying the methyl group, that is positions 2-3 and 3-4, are preferred; and until further evidence is forthcoming and the synthesis accomplished, cadinene may be regarded as having one or other of these structures (III.) or as being a mixture of the two hydrocarbons, referred to as  $\alpha$ - and  $\beta$ -cadinene,



Closely related to cadinene is the sesquiterpene alcohol cadinol<sup>1</sup> which is found in galbanum oil. By the loss of a molecule of water, cadinol is converted into cadinene, so that it evidently contains the cadalene skeleton. Since the hydroxyl group of cadinol fails to interact with phthalic anhydride, it may be inferred that cadinol is a tertiary alcohol.

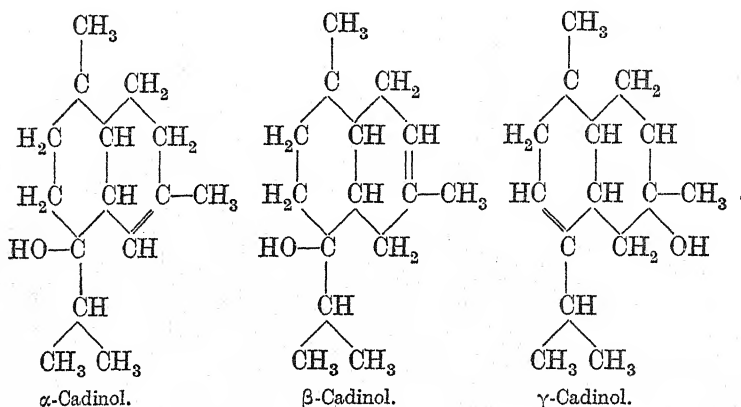
With some difficulty, cadinol was reduced to dihydrocadinol by means of hydrogen and platinum black; and on boiling the dihydro-derivative with 90 per cent. formic acid, a dihydro-cadinene was produced.

On ozonizing this dihydrocadinene, a keto-aldehyde and a keto-acid were produced by the disruption of the remaining

<sup>1</sup> Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, 7, 94.

single bond. By ozonizing cadinene itself, a compound  $C_{15}H_{24}O_2$  was obtained, which was conjectured to be an unsaturated keto-alcohol. This substance when treated with 95 per cent. formic acid yielded a ketone  $C_{15}H_{22}O$ , containing two double bonds. On oxidation with manganese dioxide and sulphuric acid, this ketone yielded only prehnitic acid.

In order to account for these rather confusing results, Ruzicka and Stoll suggested that "cadinol" is really a mixture of three substances corresponding to the formulæ shown below. It will be seen that even this does not entirely clear away the whole of the problem's difficulties.



The action of concentrated formic acid upon cadinene has been studied independently by Robertson, Kerr, and Henderson.<sup>1</sup> The chief product was found to be a sesquiterpene (or mixture of sesquiterpenes) which refused to form any stable compound with hydrochloric acid.

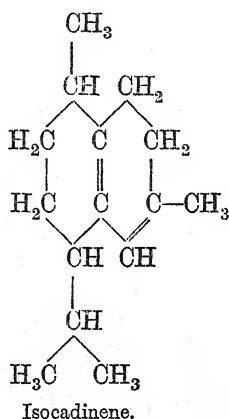
On heating cadinene with glacial acetic and sulphuric acids, Henderson and Robertson<sup>2</sup> obtained an isocadinene, which seems to be produced also by heating cadinene in a sealed tube with glacial acetic acid. This last product easily resinified in air, decolorized permanganate solution and absorbed bromine with the liberation of hydrogen bromide. It refused to yield a solid

<sup>1</sup> Robertson, Kerr, and Henderson, *J.*, 1925, 127, 1944.

<sup>2</sup> Henderson and Robertson, *J.*, 1924, 125, 1992.

nitrosochloride, nitrosite, or nitrosate. Further investigation<sup>1</sup> has shown that this isocadinene is probably identical with a sesquiterpene previously obtained from cade oil<sup>2</sup> and differs from cadinene only in the positions of the double bonds. The physical properties of isocadinene show so close a resemblance to those of one of the hydrocarbons synthesized by Ruzicka and Capato, as mentioned above, that it seems almost certain that all three compounds have a common structure.

Henderson and Robertson suggest the following formula for isocadinene:



#### F.—ZINGIBERENE<sup>3</sup>

This sesquiterpene, found in ginger oil, presents certain points of interest owing to sundry anomalies in its behaviour. Its molecular refraction is 68.37, which obviously lies between the values 69.60 and 67.87, which have been calculated for an open-chain and a monocyclic sesquiterpene. It ought therefore to have in its structure at least three, and possibly four, double bonds. In practice, however, it takes up only two molecules of hydrogen chloride; and it refuses to form a trihydrochloride.

<sup>1</sup> Henderson and Robertson, *J.*, 1926, 129, 2811.

<sup>2</sup> Tröger and Feldmann, *Arch. Pharm.*, 1898, 236, 692.

<sup>3</sup> Semmler and Becker, *Ber.*, 1913, 46, 1814; Ruzicka, Meyer, and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 359; Ruzicka and Veen, *Annalen*, 1929, 468, 143.



Further, it was found impossible to regenerate zingiberene from the dihydrochloride.

A partial explanation of these anomalies is to be found on the basis of two assumptions. First, if zingiberene is a monocyclic sesquiterpene containing two conjugated double bonds, the well-known optical effect of conjugation might tend to raise its refractivity above the normal calculated value for this class. Secondly, under the action of hydrochloric acid, zingiberene might become converted into a dicyclic structure by ring-closure ; and this new isozingiberene might not be reconvertible into the original hydrocarbon.

In the first place, it is necessary to prove that in zingiberene there are actually three double bonds. This has been done by reducing the hydrocarbon with hydrogen in presence of platinum black, whereby hexahydro-zingiberene,  $C_{15}H_{30}$ , is formed. From this it is clear that zingiberene is actually a monocyclic sesquiterpene.

Secondly, it is necessary to clear up the question of the possible conjugation of the bonds in the zingiberene structure. On reducing zingiberene with sodium and alcohol, two hydrogen atoms are attached to the molecule, producing dihydro-zingiberene,  $C_{15}H_{20}$ . The molecular refraction of this dihydro-derivative was found to be 68.36, whilst the calculated value, on the basis of two isolated double bonds in the molecule, is 68.25. The agreement here is close enough to prove that the two double bonds in the molecule are isolated from each other ; and when it is compared with the marked divergence between observed and calculated values in the case of zingiberene itself, it is sufficient to suggest that during the reduction the conjugated system has been attacked and replaced by a single ethylenic linkage.

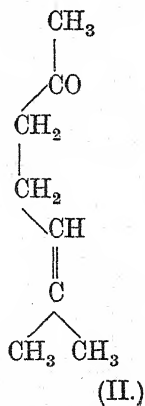
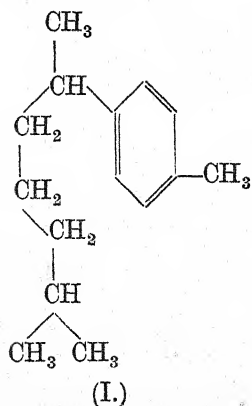
Thirdly, we must consider the conversion of zingiberene into isozingiberene. By treating zingiberene with glacial acetic acid and sulphuric acid for some hours, isozingiberene was produced. Its refractive index was found to be 66.50, whilst that calculated for a dicyclic sesquiterpene is 66.13 ; so that the agreement between the values is fair. Further, on reduction with hydrogen and platinum black, isozingiberene yields a tetrahydro-derivative instead of the hexahydro-compound obtained under similar conditions from zingiberene ; which shows that one double

bond of zingiberene has disappeared during the formation of isozingiberene. This evidence proves conclusively that isozingiberene is a dicyclic sesquiterpene.

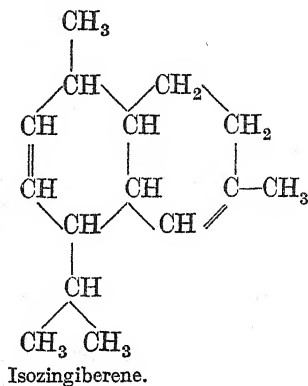
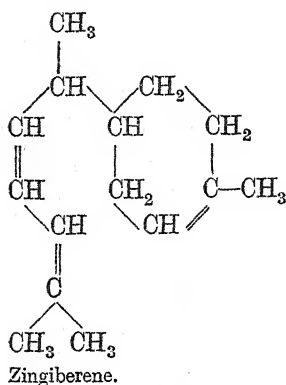
Fourthly, the question of the action of hydrogen chloride must be examined. When isozingiberene is treated with hydrogen chloride in dry ether, it yields the same dihydrochloride as that which is obtained from zingiberene itself under identical conditions. This proves that the dihydrochloride arises from isozingiberene, which has only two double bonds; and that it is formed from zingiberene itself only after a cyclization has taken place under the action of the hydrogen chloride. On treatment with alcoholic potash, the dihydrochloride regenerated isozingiberene without any accompanying zingiberene. This evidence shows definitely that zingiberene itself is converted into isozingiberene before any attachment of hydrochloric acid occurs.

Fifthly, both zingiberene and isozingiberene yield cadalene on treatment with sulphur by Vesterberg's method. This proves that both the monocyclic and dicyclic hydrocarbon have the cadalene skeleton as their bases.

Sixthly, when hexahydro-zingiberene is dehydrogenated by passing it over palladised charcoal,  $\zeta$ -*p*-tolyl- $\beta$ -methylheptane (I.) is formed, which on oxidation with chromic acid yields acetic, oxalic, and terephthalic acids. The dehydrogenation product (I.) has been synthesized by acting on methyl-heptenone (II.) with magnesium *p*-tolyl bromide and subsequently subjecting the resulting compound to dehydration and catalytic reduction.



Fitting together the foregoing evidence, the following structures may be ascribed to zingiberene and isozingiberene :



The position of the methyl group in the side-chain of zingiberene (and that of the corresponding methyl radicle in the isozingiberene formula) is not the same as that which was proposed by Semmler. He placed the methyl group on the adjacent atom of the side-chain; but obviously his proposed structure could not yield cadalene.

It will be seen from the foregoing that the zingiberene problem presents some points of interest; and that it illustrates the manner in which refractive index can be utilized as an aid in the field of the sesquiterpenes.

#### G.—THE SELINENES

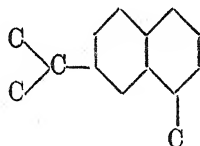
The compounds hitherto discussed in this chapter have all been based on the cadalene skeleton; but with the selenenes we reach the eudalene group.

Celery-seed oil contains a sesquiterpene originally termed selinene, but now known as  $\beta$ -selinene in order to distinguish it from an isomeric hydrocarbon which is obtained from it in the following way. Like cadinene,  $\beta$ -selinene yields a bis-hydrochloride; and by careful treatment of this hydrochloride with caustic soda in methyl alcohol solution, an isomer of natural selinene is produced. This  $\alpha$ -selinene, as it is termed, unites with hydrochloric acid again to form the same bis-hydro-

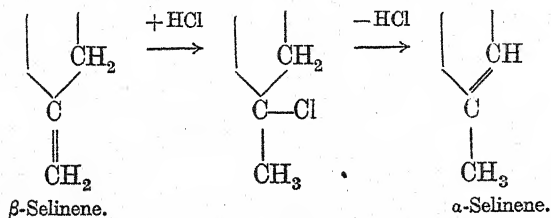
chloride as is obtained from  $\beta$ -selinene; but the two hydrocarbons are not identical, being structurally isomeric with each other.

This is easily proved from the results of ozonization.<sup>1</sup> The  $\beta$ -selinene gives a good yield of a diketone,  $C_{13}H_{20}O_2$ , along with minor quantities of acidic oxidation-products. The  $\alpha$ -selinene, on the other hand, produces only a small yield of this ketone; and its main product is a carboxylic acid,  $C_{14}H_{22}O_4$ . On further oxidation with alkaline bromine solutions, both the ketone and the dicarboxylic acid are converted into the same tricarboxylic acid,  $C_{12}H_{18}O_6$ .

When treated with sulphur by the Vesterberg method<sup>2</sup> both selinenes yield eudalene; so that both of them contain the skeleton:



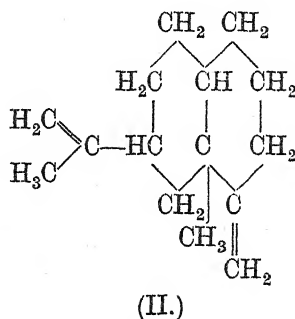
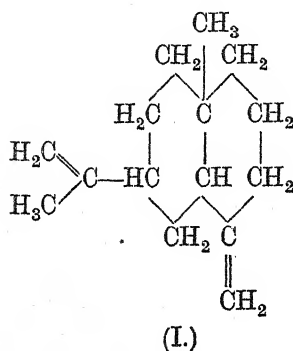
In order to account for the convertibility of  $\beta$ -selinene into  $\alpha$ -selinene through a bishydrochloride common to both compounds, the simplest assumption is that the difference between the two sesquiterpenes is merely in the position of a double bond with respect to one carbon atom in the molecule. In  $\alpha$ -selinene, the bond is supposed to be in the ring; whilst in  $\beta$ -selinene it is assumed to unite a methylene group to the rest of the molecule:



<sup>1</sup> Semmler and Risse, *Ber.*, 1912, 45, 3301, 3725.

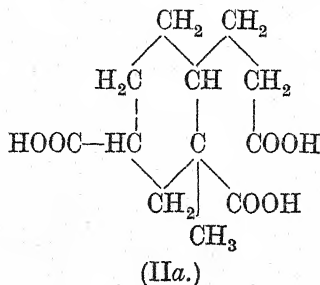
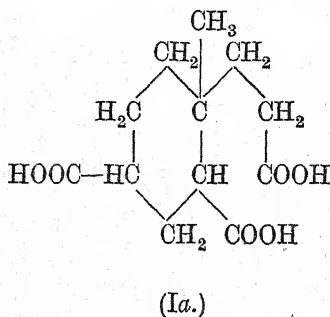
<sup>2</sup> Ruzicka, Meyer, and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 345.

If this view be adopted, it helps to make clear one of the difficulties of the selinene problem; but we have still to define the position of the methyl group which disappears during the conversion of selinene into eudalene. Two positions are possible for this group, as was pointed out in an earlier section of this chapter; so that even on the above assumptions, natural selinene may be either (I.) or (II.).



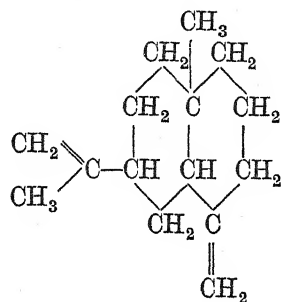
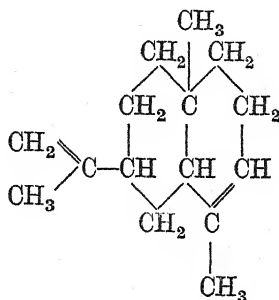
When  $\alpha$ -selinene is boiled with alcoholic sulphuric acid, the double bond of the isopropylene group apparently migrates into the ring and a mixture of two substances is formed. These have been termed  $\delta$ - and  $\epsilon$ -selinene.<sup>1</sup>

The oxidation of (I.) would yield a tricarboxylic acid (Ia.), whilst the oxidation of (II.) would yield an acid of the structure (IIa.).



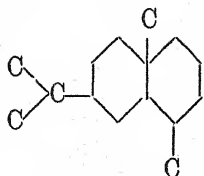
<sup>1</sup> Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, 6, 846.

Now the actual tricarboxylic acid obtained from both forms of selinene is easily esterified<sup>1</sup> to a tri-ester. An acid of formula (IIa.), on the contrary, would be subject to steric hindrance owing to one of the  $\text{—COOH}$  groups being attached to a tertiary carbon atom. The evidence, therefore, is in favour of the tricarboxylic acid having the formula (Ia.); and hence the position of the eliminated methyl group is probably as shown in formula (I.). The structures of the two selinenes are thus, in all likelihood, those which are shown below :

 $\beta$ -Selinene. $\alpha$ -Selinene.

#### H.—EUDESMOL

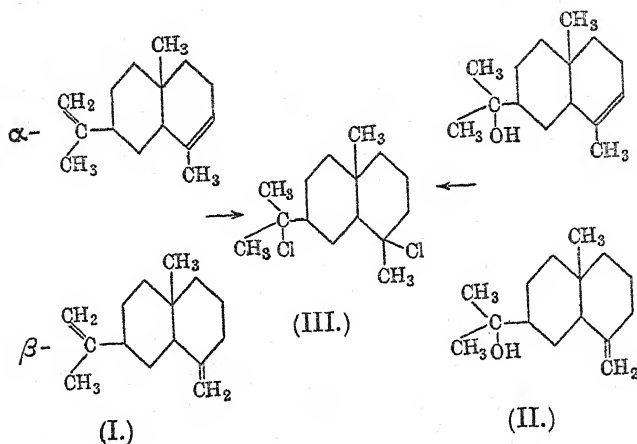
The structure of this sesquiterpene alcohol from eucalyptus has been settled in the following manner.<sup>2</sup> Its properties indicate that it is a dicyclic tertiary alcohol containing one double carbon bond. Application of the Vesterberg method proves that eudesmol has the same carbon skeleton as that of selinene :—



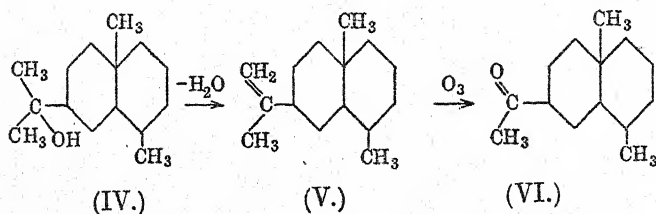
<sup>1</sup> Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, 6, 846.

<sup>2</sup> Ruzicka and Capato, *Annalen*, 1927, 453, 62; Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, 1931, 14, 1132.

The relationship between the selinenes (I.) and eudesmol (II.) was demonstrated to be still closer when from each the same dihydrochloride (III.) was obtained.



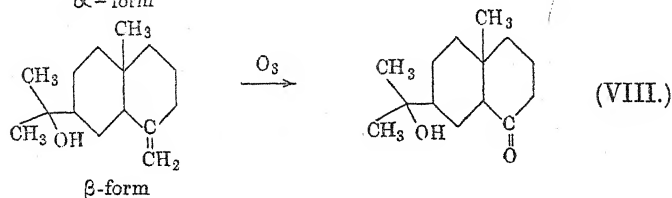
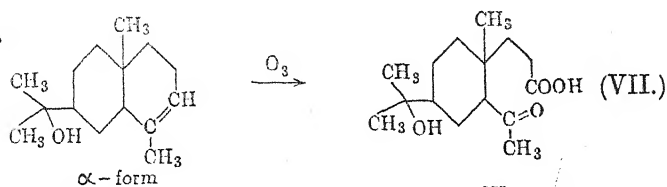
This limits the number of possible positions for the double bond and the hydroxyl group. Eudesmol forms a benzoyl derivative with ease. A hydroxyl group directly connected to a ring does not readily react in this way.<sup>1</sup> This points to the tertiary alcoholic group being attached to the isopropyl group. This was confirmed by the production of 6-acetyl-4:9-dimethyl decahydronaphthalene (VI.) from dihydroeudesmol (IV.) by dehydration under very mild conditions to the unsaturated hydrocarbon (V.) followed by ozonization.



Eudesmol, like its relative selinene is a mixture of  $\alpha$ - and  $\beta$ -forms, as ozonolysis yields both an oxyketo acid (VII.) and an oxyketone (VIII.).

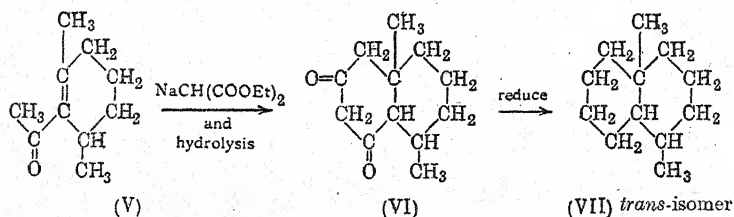
<sup>1</sup> Ruzicka and van Veen, *Annalen*, 1929, 476, 109.



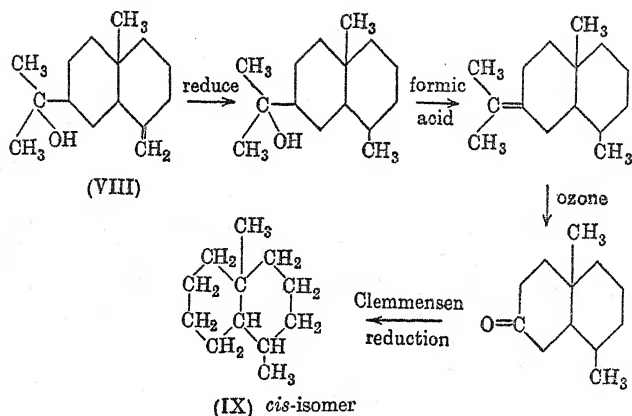


The production of the oxyketo acid (VII.) without the loss of any carbon atoms demonstrates the presence of a ring double bond in the molecule, and the formation of the oxyketone (VIII.) by the loss of one carbon atom from eudesmol indicates clearly that here the double bond lies in the side chain. The eudesmol prepared from selinene is largely the  $\alpha$ -compound, whilst the  $\beta$ -form predominates in the oil from *Eucalyptus Macarthurii*.

Decahydronaphthalene (decalin) derivatives such as selinene and eudesmol may possibly also exist in *cis*- and *trans*-forms (see volume III, Chap. X), and this problem of stereoisomerism has been successfully investigated.<sup>1</sup> A number of *trans*-tetrahydronaphthalene homologues have been synthesized by known methods from the simpler hexane derivatives. Thus *trans*-4 : 9-dimethyldecahydronaphthalene (VII.) was synthesized from 2 : 6-dimethyl- $\Delta^1$ -cyclohexenyl methyl ketone (V.) through the diketone-compound (VI.), and some of its physical properties compared with the 4 : 9-compound (IX.) obtained by degrading eudesmol (VIII.). In treating the sesquiterpene derivatives, reactions likely to bring about rearrangement of the decahydronaphthalene ring were avoided.



<sup>1</sup> Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, 1931, 14, 1151, 1171; Kon and Qudrat-i-Khuda, *J.*, 1926, 3071.



In similar ways *trans*-5:9-dimethyl-3-ethyldecahydronaphthalene and other *trans*-compounds were synthesized and compared with the corresponding derivatives from eudesmol. It was shown that the sesquiterpene derivatives had, in all the examples examined, the *cis*-configuration.

### I.— $\alpha$ -SANTALOL

Sandalwood oil contains a large number of ethereal oils such as santene,  $C_9H_{14}$ , teresantalol,  $C_{10}H_{16}O$ , the santalenes,  $C_{15}H_{24}$ , and  $\beta$ - and  $\alpha$ -santalol. In the present section the constitution of this last substance will be discussed.<sup>1</sup> To save continual repetition, the  $\alpha$ - will be omitted and the compound will be referred to simply as santalol.\*

Santalol has the formula  $C_{15}H_{24}O$ . On oxidation with chromic acid, it yields an aldehyde, santalal,  $C_{14}H_{21}CHO$ . This proves santalol to be a primary alcohol.

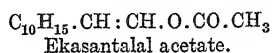
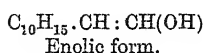
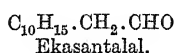
Further oxidation converts santalal into a lower aldehyde, ekasantalal,  $C_{11}H_{17}CHO$ , which is also obtained direct from santalol by ozonization. This indicates that santalol has three carbon atoms separated from the rest of its structure by a double bond which is attacked by the ozone.

<sup>1</sup> Semmler and others, *Ber.*, 1907, 40, 1120; 1908, 41, 1488; 1909, 42, 584; 1910, 43, 1722, 1890; 1913, 46, 2300.

\* The reader is advised to consult the scheme on p. 148 as an aid to the comprehension of this section.

From ekasantalal, through its oxime and nitrile, the acid  $C_{11}H_{17} \cdot COOH$ , ekasantalic acid, is obtained, which can also be produced by direct oxidation of santalol with potassium permanganate. This last reaction shows that ekasantalic acid contains no double bond; for if it did, then further oxidation by the permanganate would take place. But if it contains no double bond in its structure, ekasantalic acid must be a tricyclic substance. Evidently this tricyclic system of ekasantalic acid is the kernel of the santalol structure. We shall return to it later.

On heating with acetic anhydride and sodium acetate, ekasantalal yields the acetate of its enolic form :

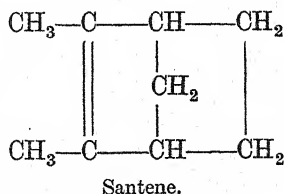


This reaction proves that ekasantalal has at least one hydrogen atom attached to the carbon carrying the aldehydic radicle, as otherwise enolization could not take place.

On oxidation, ekasantalal acetate yields *norekasantalic* acid,  $C_{10}H_{15} \cdot COOH$ , which is obviously the lower homologue of ekasantalic acid,  $C_{11}H_{17} \cdot COOH$ .

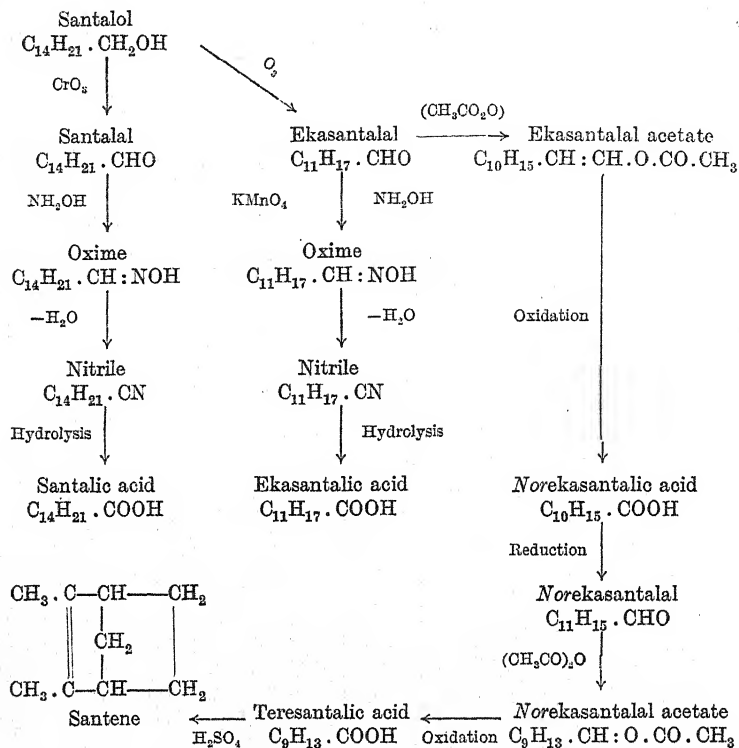
*Norekasantalic* acid on reduction yields the aldehyde *norekasantalal*,  $C_9H_{13} \cdot CH_2 \cdot CHO$ , which forms an acetate like ekasantalal and can thus be converted into *teresantalic* acid,  $C_9H_{13} \cdot COOH$ .

Finally, when *teresantalic* acid is boiled with dilute sulphuric acid, it loses carbon dioxide and is converted into *santene*,  $C_9H_{14}$ , which has been shown by synthesis<sup>1</sup> to have the following structure :—

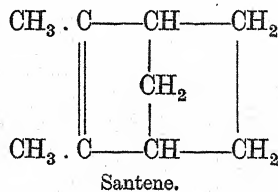


The scheme given below shows the various steps outlined in the foregoing paragraphs.

<sup>1</sup> Komppa and Hintika, *Bull. Soc. chim.*, 1917 (4), 21, 13.

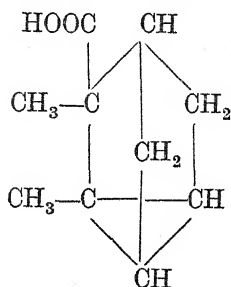


In order to establish the santalol constitution, it is now necessary to retrace these steps in the inverse order, beginning with the known constitution of santene :



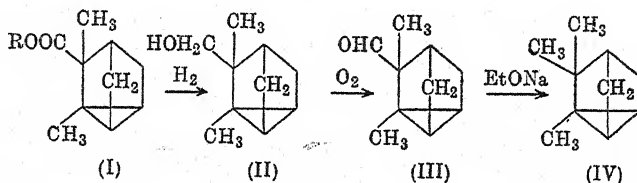
In order to pass from santene back to teresantallic acid, a carboxyl group must be fitted into the molecule. At the same time, a further condition must be fulfilled. Santene is an unsaturated compound and its double bond offers a point of attack to oxidizing agents. No such group can be present in teresantallic acid. If it were, then teresantallic acid would be oxidized as soon as it was formed during the oxidation of norekasantalal acetate.

The only plausible way of getting round this difficulty is to assume that teresantallic acid is a tricyclic substance—a conclusion supported by the refractivity of the compound. Semmler, from a complete examination of the properties of teresantallic acid, has attributed to it the structure shown below.



Teresantallic Acid.

This structure for teresantallic acid is fully supported by its relationship to tricyclene<sup>1</sup> (IV.) and to 7- $\pi$ -apocamphane-carboxylic acid (dihydroteresantallic acid) (IX.). When teresantallic acid was esterified (I.) and reduced, teresantalol (II.) was formed, and from this by the action of chromic acid the corresponding aldehyde (III.) was produced. By the Wolff method\* the aldehyde semicarbazone was reduced to tricyclene (IV.).<sup>2</sup>



The structure of tricyclene is known from its relationship to isocamphane, pinene dibromide, camphor and camphene, and consequently any doubt about the position of the carboxyl group in teresantallic acid is removed.

The conversion of teresantallic acid into 7- $\pi$ -apocamphane-carboxylic acid (dihydroteresantallic acid) has been accomplished

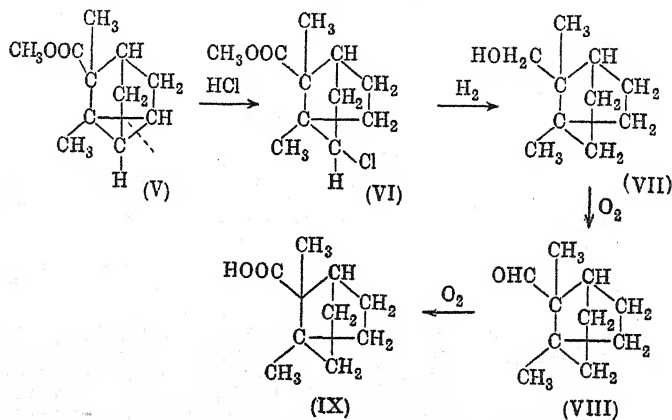
<sup>1</sup> Ruzicka and Liebs, *Helv. Chim. Acta*, 1926, 9, 140.

\* This method of reducing the  $>CO$  group to  $>CH_2$  consists in heating the semicarbazone or hydrazone of the carbonyl compound to 170° C.-180° C. with sodium ethoxide.

<sup>2</sup> Wolff, *Annalen*, 1912, 394, 90.

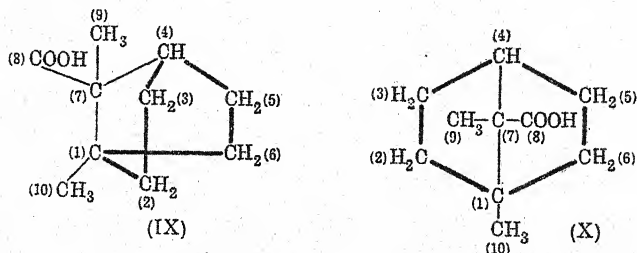
by different methods,<sup>1</sup> one of which may be described. When hydrogen chloride was added to teresantalic acid methyl ester (V.) the cyclopropane ring was opened and chlorodihydro-teresantalic ester (VI.) formed. This was reduced by means of sodium and alcohol to dihydroteresantalol ( $\pi$ -borneol) (VII.). The aldehyde (VIII.) was obtained from the alcohol and then converted into 7- $\pi$ -apocamphane-carboxylic acid (dihydro-teresantalic acid) (IX.).

The structural scheme of the changes is :—



The constitution of 7- $\pi$ -apocamphanecarboxylic acid is known from its synthesis from camphor.<sup>2</sup>

It is to be noted that formula (IX.) may be written as (X.). The two differ only in the method of plane projection. By numbering the carbon atoms and emphasizing some of the linkages by heavy lines in the two structures the identity is made clearer.



<sup>1</sup> Hasselström, *J. Amer. Chem. Soc.*, 1931, 53, 1097.

<sup>2</sup> Hasselström, *Ann. Acad. Fenn.*, 1929, 30, 12.

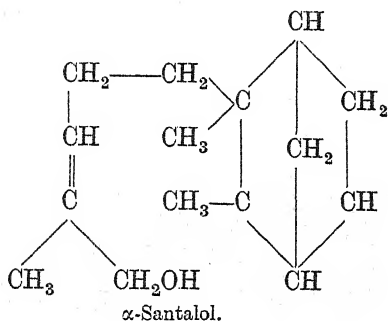
In a similar way two projections of teresantallic acid, tricyclene and  $\alpha$ -santalol may be written down.

The final part of the reconstruction is simple. Since santalol is a primary alcohol, the alcoholic radicle must lie at the extreme end of the chain which is attached to the tricyclic system.

Further, since ozone breaks off three carbon atoms from the santalol system, there must be a double bond between the third and fourth carbon atoms of the side-chain.

Lastly, this side-chain must be attached to the tricyclic system at the point where the carboxyl group lies in teresantallic acid.

This reasoning leads to the following structure for santalol :—



## J.—EREMOPHILONE AND RELATED HYDROXY-KETONES

Eremophilone, hydroxyeremophilone and hydroxydihydroeremophilone have been isolated from the wood oil of *Eremophila Mitchellii* and their structures investigated.<sup>1</sup> These compounds are of interest, as they were the first cyclic ketones of the sesquiterpene group to be discovered.

### 1. *Eremophilone*

This compound has the molecular formula  $C_{15}H_{22}O$ . It is a ketone and contains two ethylenic linkages, as it can be catalytically reduced to tetrahydroeremophilone. One of the double

<sup>1</sup> Bradfield, Penfold, and Simonsen, *J.*, 1932, 2744.

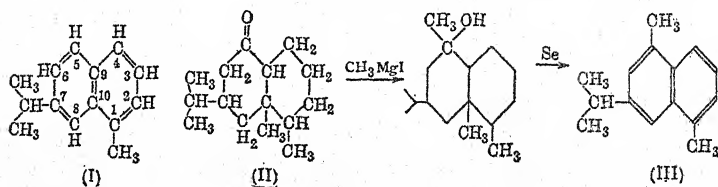


bonds is in the  $\alpha$   $\beta$  position to the carbonyl group thus;

$-\text{CO}-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}=\text{C}-$ . This grouping reacts in a characteristic way with alkaline hydrogen peroxide<sup>1</sup> and eremophilone follows the general rule in giving an oxide,  $-\text{CO}-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}-$ . That the

ethylenic linkage is conjugated with the carbonyl group is further supported by the facts that eremophilone forms a compound with hydrogen sulphide, and has an absorption spectrum typical of a compound containing a conjugated system of double bonds.<sup>2</sup> Eremophilone yields an hydroxymethylene derivative and so a further constitutional step may be taken, and a methylene group

placed adjacent to the carbonyl group,  $-\text{CH}_2-\text{CO}-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}=\text{C}-$ . On reduction to the alcohol, dihydroeremophilol,  $\text{C}_{15}\text{H}_{26}\text{O}$  and subsequent dehydrogenation with selenium, it yields the naphthalene hydrocarbon, eudalene (I.), one carbon atom being eliminated during the process. This gives us the main outline of the carbon framework of the molecule. Subsequent evidence indicates that the remaining carbon atom is attached at the angle position 10.



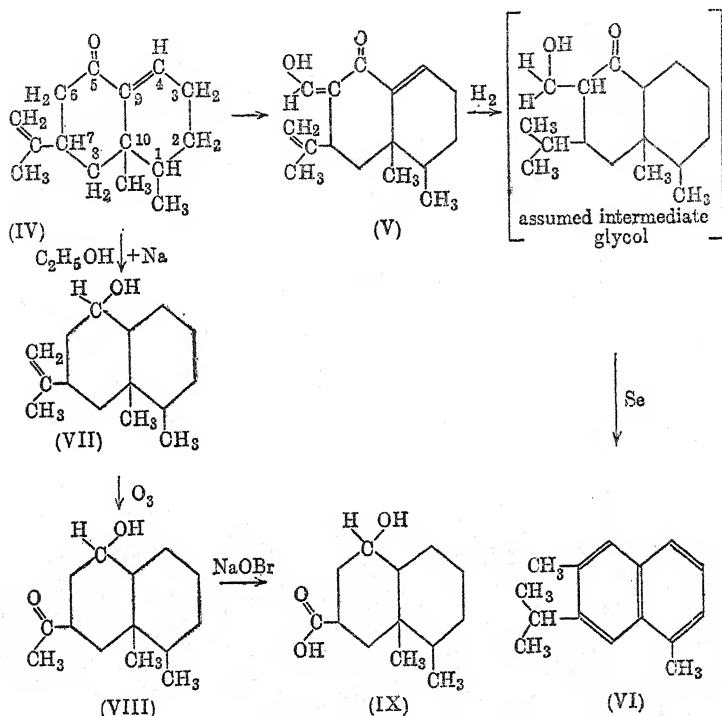
When tetrahydroeremophilone (II.) is treated with methyl magnesium iodide and then dehydrogenated with selenium, it yields 1:5-dimethyl-7-isopropynaphthalene (III.) as shown above.<sup>3</sup> The carbonyl group of eremophilone is therefore situated at position 5. This orientation is confirmed by the conversion of hydroxymethylene-eremophilone (V.) into 1:6-

<sup>1</sup> Weitz and Scheffer, *Ber.*, 1921, 54, 2327.

<sup>2</sup> Gillam, *J.*, 1936, 676.

<sup>3</sup> Bradfield, Pritchard, and Simonsen, *J.*, 1937, 760; *J.*, 1938, 767.

dimethyl-7-isopropynaphthalene (VI.) by reduction and dehydrogenation as follows.



The alcohol, dihydroeremophilol,  $\text{C}_{15}\text{H}_{26}\text{O}$  (VII.), on oxidation with ozone, gives formaldehyde and an hydroxy-ketone,  $\text{C}_{14}\text{H}_{24}\text{O}_2$  (VIII.). Further oxidation using sodium hypobromite yields an hydroxy-acid,  $\text{C}_{13}\text{H}_{22}\text{O}_3$  (IX.) and bromoform. This step by step degradation of dihydroeremophilol may be

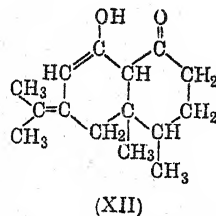
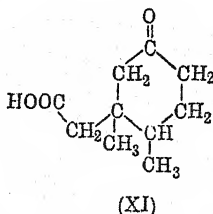
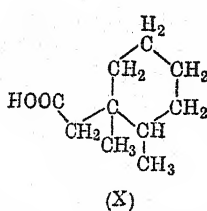
interpreted by assigning the isopropenyl,  $\text{CH}_3-\text{C}(\text{CH}_3)=\text{CH}_2$ , structure to one of the side chains of eremophilone as above. It is obvious that this point of unsaturation cannot be the ethylenic linkage adjacent to the carbonyl group. The double bond conjugated with the carbonyl group must be at the position 4-9 as position 6 carries a  $\text{CH}_2$  group and position 10 a methyl group. Structure (IV.) may therefore be assigned provisionally to eremophilone.

2. *Hydroxyeremophilone*

Eremophilone oxide when digested with acetic acid and sodium acetate<sup>1</sup> and then warmed with alkali yields, through its benzoyl derivative, hydroxyeremophilone identical with the natural compound. When hydroxyeremophilone benzoate is oxidized with ozone it yields more acetone than formaldehyde. It is therefore concluded that it occurs chiefly in the form having

an isopropylidene,  $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C} = \\ \diagdown \\ \text{CH}_3 \end{array}$ , side-chain. The prolonged oxida-

tion of hydroxyeremophilone benzoate with ozone yields a keto-acid,  $\text{C}_{10}\text{H}_{16}\text{O}_3$ , which may be reduced by Clemmensen's method to a saturated acid,  $\text{C}_{10}\text{H}_{18}\text{O}_2$ . The methyl ester of this saturated acid is converted into ortho-xylene when dehydrogenated with selenium. The acid must therefore have the structure<sup>2</sup> (X.) and the keto-acid,  $\text{C}_{10}\text{H}_{16}\text{O}_3$  will be (XI.). From the information at present available a possible structure for hydroxyeremophilone is (XII.).<sup>2</sup>

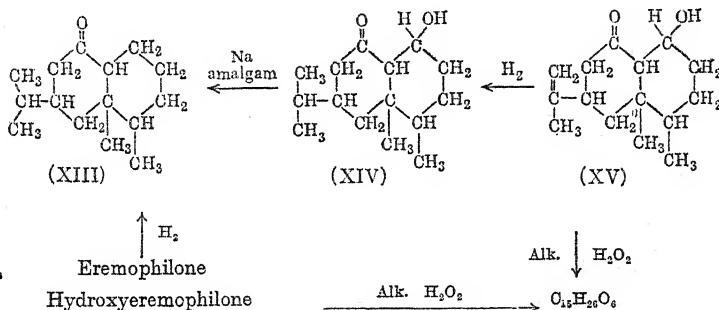
3. *Hydroxydihydroeremophilone*

This compound gives the reactions of an hydroxy-ketone containing one double carbon bond. It yields eudalene after reduction and treatment with selenium. Oxidation with ozone produces formaldehyde and traces of acetone. On catalytic reduction it takes up one molecule of hydrogen and passes into hydroxytetrahydroeremophilone (XIV.), which on further reduction with sodium amalgam yields tetrahydroeremophilone (XIII.) identical with the compound obtained from eremophilone

<sup>1</sup> Bradfield, Hellström, Penfold, and Simonsen, J., 1938, 767; *Ann. Reports*, 1938, 276.

<sup>2</sup> Penfold and Simonsen, J., 1939, 87.

itself by catalytic reduction. Oxidation of hydroxydihydro-eremophilone with alkaline hydrogen peroxide yields a dihydroxydicarboxylic acid,  $C_{15}H_{26}O_6$ , which can also be isolated from the oxidation products of hydroxyeremophilone. All these facts point to a very close relationship between hydroxydihydro-eremophilone on the one hand and eremophilone and hydroxyeremophilone on the other. The following scheme shows the connection between the three compounds and a possible structure (XV.) for hydroxydihydroeremophilone.



## K.— $\alpha$ - AND $\beta$ -CYPERONE

### 1. General

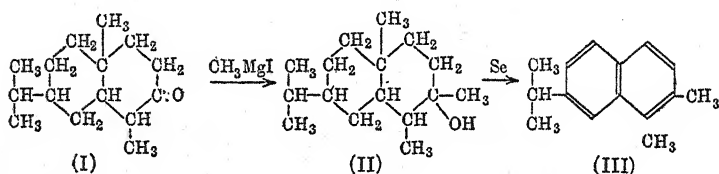
$\alpha$ -Cyperone is the chief constituent of the higher-boiling fractions from oil of *Cyperus rotundus*.<sup>1</sup> It closely resembles eremophilone in a number of its chemical reactions, but is of special interest as compounds structurally identical with it and derivatives have been synthesized. These syntheses are the only direct evidence so far obtained of the presence of a methyl group at the angle position 9 in the sesquiterpenes which yield eudalene on dehydrogenation.

### 2. The Degradation Products and Structure of $\alpha$ -Cyperone

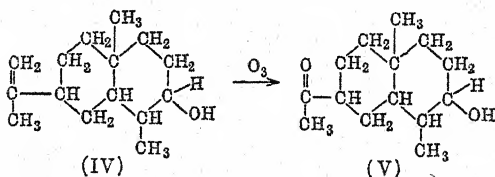
$\alpha$ -Cyperone is a dicyclic ketone containing two double carbon bonds. It can be reduced with sodium and alcohol to dihydro- $\alpha$ -cyperol (IV.), which by the action of selenium yields eudalene,

<sup>1</sup> Hegde and Rao, *J. Soc. Chem. Ind.*, 1935, 54, 387 T.

and by the action of ozone produces formaldehyde and a keto-alcohol (V.). The 3 : 5-dinitro-benzoate of  $\alpha$ -cyperol with ozone yields a ketone from which Fuson's reagent \* splits off iodoform.<sup>1</sup> On catalytic reduction  $\alpha$ -cyperone is converted into tetrahydro- $\alpha$ -cyperone (I.). This latter compound may be transformed by interaction with methyl magnesium iodide into the corresponding tertiary alcohol (II.), which yields 1 : 2-dimethyl-7-isopropyl-naphthalene (III.) on dehydrogenation.<sup>2</sup> This shows that position 2 in the carbon framework of  $\alpha$ -cyperone is occupied by the keto-group.<sup>1</sup> The structure of tetrahydro- $\alpha$ -cyperone must therefore be (I.). The changes to the naphthalene derivative may be represented as follows :—



It follows that dihydro- $\alpha$ -cyperol must be the related isopropenyl derivative (IV.), as this structure alone explains the formation of the ketone (V.), which yields iodoform with Fuson's reagent.



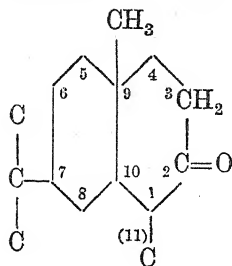
The second ethylenic linkage in  $\alpha$ -cyperone is either conjugated with that in the isopropenyl group or with the carbonyl group, as it is reduced by sodium and alcohol. The conjugation of the two ethylenic linkages is very improbable on account of the resistance to reduction by sodium and alcohol of the hydrocarbon  $\alpha$ -cyperene obtained from  $\alpha$ -cyperone. No direct proof, however, is forthcoming of conjugation with the carbonyl group.

\* This reagent contains dioxan, sodium hydroxide, iodine and potassium iodide, and is a modification of the solution used in the well-known iodoform test for alcohols and ketones.

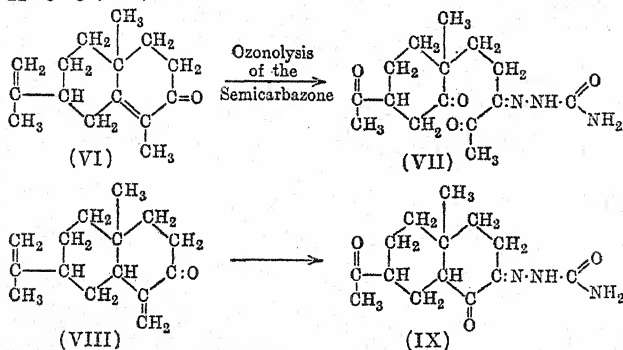
<sup>1</sup> Fuson and Tullock, *J. Amer. Chem. Soc.*, 1934, **56**, 1638.

<sup>2</sup> Bradfield, Hegde, Rao, Simonsen and Gillan, *J.*, 1936, 667.

An oxide such as is obtained from eremophilone cannot be isolated, and no derivative is obtained with hydrogen sulphide in the presence of alcoholic ammonia. The hydroxymethylene derivative of  $\alpha$ -cyperone after reduction and dehydrogenation yields 1:3-dimethyl-7-isopropyl-naphthalene, proving the presence of a methylene group adjacent to the carbonyl group. This can only be at position 3. The double carbon bond conjugated with the carbonyl group cannot, therefore, be at position 3-4. This leaves two possible positions for the double carbon bond, either at 1-10 or 1-11. A choice can be made between



these two possibilities by considering the evidence obtained from the ozonolysis of  $\alpha$ -cyperone semicarbazone.<sup>1</sup> If  $\alpha$ -cyperone has the structure (VI.) the product of ozonolysis of the semicarbazone should be a compound with the molecular formula  $C_{15}H_{23}O_4N_3$  (VII.). On the other hand if  $\alpha$ -cyperone is (VIII.) the compound obtained would have the composition  $C_{14}H_{21}O_3N_3$  (IX.)



Oxidation of  $\alpha$ -cyperone semicarbazone with ozone gave a compound which by analysis had the formula  $C_{15}H_{23}O_4N_3$ .

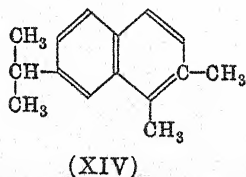
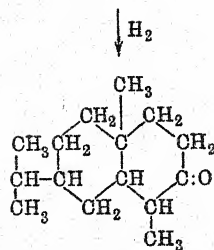
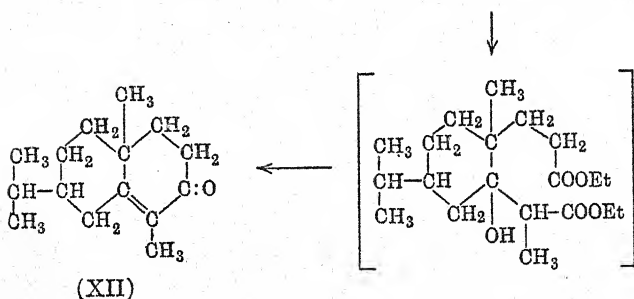
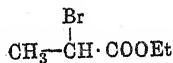
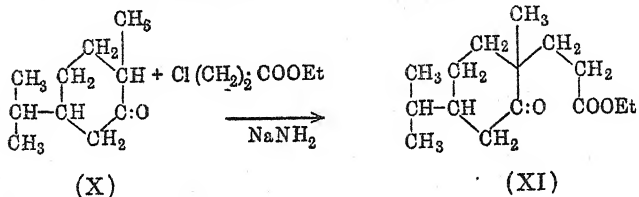
<sup>1</sup> Bradfield, Pritchard, and Simonsen, *J.*, 1937, 760.

Structure (VII.) is assigned to this substance, and consequently  $\alpha$ -cyperone is formulated as (VI.).

### 3. The Structure of $\beta$ -Cyperone

When  $\alpha$ -cyperone is treated with hydrogen peroxide in alkaline solution or by aqueous oxalic acid it is converted into  $\beta$ -cyperone; and since the semicarbazones of both yield the same product of ozonolysis they are looked upon as stereoisomerides, differing in the dispositions of the angle methyl and the isopropenyl groups.

### 4. The Syntheses of the Cyperones

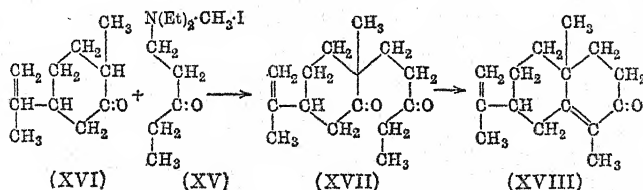




We may now turn to the evidence afforded by the syntheses of the cyperones and their derivatives.<sup>1</sup>

When *l*-tetrahydrocarvone (X.) was condensed with ethyl  $\beta$ -chloropropionate in the presence of sodamide the compound (XI.) was formed. This ester by the Reformatsky reaction, using ethyl  $\alpha$ -bromopropionate, yielded the unsaturated dicyclic ketone,  $C_{15}H_{24}O$  (XII.). This compound was catalytically hydrogenated (XIII.) and converted via the Grignard reaction, and dehydrogenation into 1:2-dimethyl-7-*isopropyl*naphthalene (XIV) identical with that obtained from natural  $\alpha$ -cyperone. When the starting material is *l*-dihydrocarvone, containing the isopropenyl group, a similar synthesis leads to a ketone closely resembling  $\beta$ -cyperone. The steps in the synthesis may be formulated as shown on p. 158.

Finally another synthesis may be recorded. The methiodide of 1-diethylaminopentan-3-one (XV.) and the sodio-derivative of *l*-dihydrocarvone (XVI.) were condensed to give the diketone (XVII.). This compound was dehydrated and cyclized by sodium ethoxide in benzene solution with the formation of  $\alpha$ -cyperone (XVIII.). With cold 50 per cent. sulphuric acid  $\beta$ -cyperone was formed.



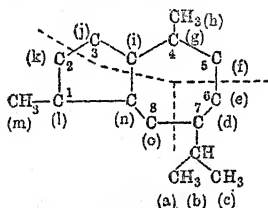
A comparison of a number of the physical properties of the synthetic cyperones with those of the compounds from natural sources points undoubtedly to structural identity. It is evident that these syntheses and the identity of the naphthalene derivative (XIV.) obtained with that from natural cyperone are strong confirmation of the correctness of the structure assigned to  $\alpha$ -cyperone.

<sup>1</sup> Bradfield, Jones, and Simonsen, *J.*, 1936, 1137; Adamson, McQuillan, Robertson, and Simonsen, *J.*, 1937, 1576.

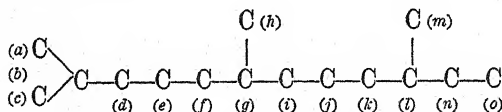
## L.—AZULENES

## 1. General

These compounds are of special interest, as they have been formulated as containing the *cyclopentane-cycloheptane* skeleton. S-guaiacazulene is regarded as being 1:4-dimethyl-7-*iso*-propylazulene, containing five double carbon bonds, the positions of which have not been finally fixed.



Inspection of this structure shows that it contains three isopentane skeletons, and if the "head to tail" union of these groups is assumed thus,



the structure suggested for S-guaiacazulene is one of the possible arrangements.

Azulenenes may be separated from oil of chamomile and oil of geranium by shaking an ethereal solution of the oil with strong phosphoric acid solution.<sup>1</sup>

Many other essential oils contain or give rise to similar blue or violet substances. A considerable amount of work has recently been done on these compounds and several isomeric azulenes identified.<sup>2</sup> They are hydrocarbons having the molecular formula,  $C_{15}H_{18}$ . The substance obtained from oil of chamomile has been named chamazulene and that from guaiol by dehydrogenation, S-guaiacazulene.<sup>3</sup> All the azulenes yield decahydro-compounds, and also from measurements of their refractivities it is concluded that they contain a dicyclic system and five double bonds.

<sup>1</sup> Sherndal, *J. Amer. Chem. Soc.*, 1915, 37, 167, 1537.

<sup>2</sup> Pfau and Plattner, *Helv. Chim. Acta*, 1936, 19, 858; Plattner and Pfau, *ibid.*, 1937, 20, 224.

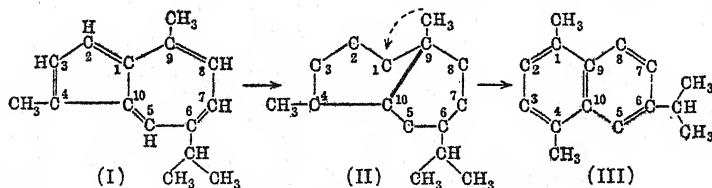
<sup>3</sup> Ruzicka and Rudolph, *Helv. Chim. Acta*, 1926, 9, 118; Ruzicka and Haagen-Smit, *ibid.*, 1931, 14, 1104, 1122.

## 2. The Degradation Products and Structures of the Azulenes

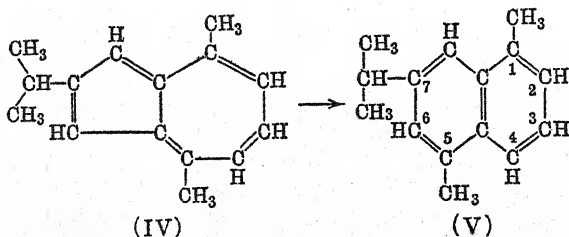
Guaïol after reduction with hydriodic acid and red phosphorus followed by dehydrogenation with sulphur yielded an azulene fraction and some 1:4-dimethyl-6-isopropyl-naphthalene. Similar treatment of Java vetiver oil gave 1:5-dimethyl-7-isopropyl-naphthalene. The conclusion that the azulenes contain the eudalene dicyclic system has been rejected on the grounds that completely reduced eudesmol derivatives give naphthalenes but no azulenes on dehydrogenation.

Oxidation of reduced S-guaïacazulene gives rise to a dibasic acid containing all fifteen carbon atoms of the original azulene. The formation of this acid is the outcome of ring-fission, and from it a ketone containing fourteen carbon atoms in the molecule is obtained. Dehydrogenation of the ketone yielded a phenolic compound; a series of changes which can be explained on the assumption that a seven-membered carbon ring was present in the original azulene.

It is suggested that the production of 1:4-dimethyl-6-isopropyl-naphthalene (III.) from S-guaïacazulene (I.) is by intramolecular rearrangement involving the transfer of a methyl-group as shown below,

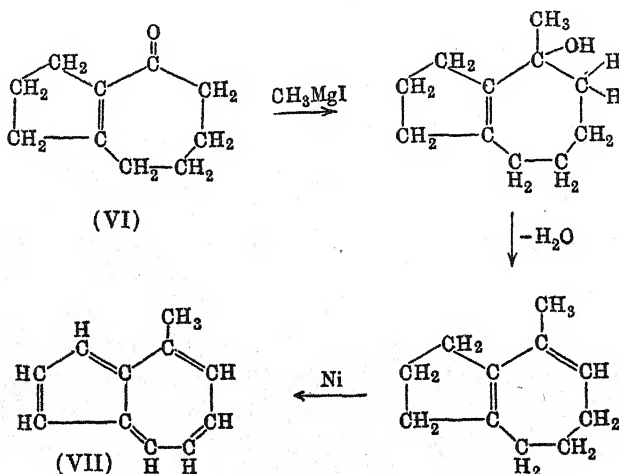


By similar changes vetivazulene, which is said to have the skeleton (IV.), is regarded as yielding 1:5-dimethyl-7-isopropyl-naphthalene (V.).

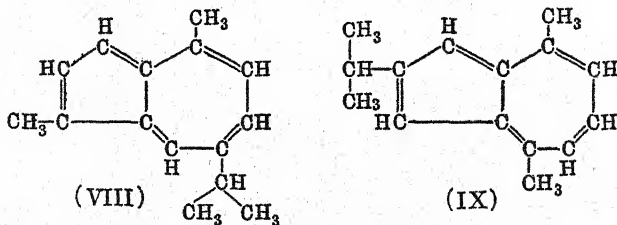


## 3. The Synthetic Azulenes

These conclusions on the problem of the structures of the azulenes receive support from syntheses of related compounds. When the *cyclopenteno-cycloheptanone* (VI.) was condensed with methyl magnesium iodide and the end-product dehydrogenated by nickel, an azulene type of compound (VII.) was formed. The structure shown was given to this substance, 4-methylazulene.



Azulene itself and other 4-substituted azulenes have been prepared in a similar way. Comparisons of the absorption spectra and other physical properties of the synthetic and natural azulenes lead to the conclusion that they all are of the same type. The positions of the double bonds have not been fixed with certainty, but the provisional structures (VIII.) and (IX.) have been given to S-guaiacazulene and vetivazulene.



## M.—THE CARYOPHYLLENES

## 1. General

Eugenol occurs in the buds of *Eugenia caryophyllata* Thunb., from which oil of cloves may be obtained. In addition to eugenol Wallach and Walker<sup>1</sup> isolated a second terpene fraction to which they gave the name caryophyllene. By the action of nitrosyl chloride Deussen<sup>2</sup> obtained from "natural caryophyllene" two independent nitrosochlorides, one of which was optically inactive, the other optically active. Thus "natural caryophyllene" is a mixture of at least two hydrocarbons, inactive  $\alpha$ -caryophyllene and laevorotatory  $\beta$ -caryophyllene. By the action of sodium nitrite and acetic acid the  $\beta$ -caryophyllene fraction yields a nitrosite, which on boiling with alcohol is converted into  $\gamma$ -caryophyllene. This hydrocarbon is probably present also in the "natural" oil. No one of the three substances has yet been isolated in the pure state and consequently interpretations of experimental results have at times been extremely difficult. Well-defined crystalline derivatives have, however, been prepared and investigated. The chief constituent of clove oil appears to be  $\beta$ -caryophyllene. On heating "natural caryophyllene" with glacial acetic and dilute sulphuric acids, hydration occurs and the product is caryophyllene alcohol, which on dehydration yields a fresh hydrocarbon clovene.<sup>3</sup> By a modification of the dehydration process another hydrocarbon, isoclovene, has been isolated.<sup>4</sup> The molecular formula of each of the five hydrocarbons is  $C_{15}H_{24}$ .

With regard to the number of rings in each of these compounds, the evidence is fairly clear. A dicyclic sesquiterpene,  $C_{15}H_{24}$ , must contain two double bonds in its structure; whilst a tricyclic one has only a single bond. Now  $\alpha$ -caryophyllene forms a nitrosochloride, by which process one double bond is saturated; and this nitrosochloride takes up one molecule of halogen acid, proving the presence of a second double bond in the molecule.<sup>5</sup> The nitrosite of  $\beta$ -caryophyllene is obviously

<sup>1</sup> Wallach and Walker, *Annalen*, 1892, 271, 283.

<sup>2</sup> Deussen, *Annalen*, 1907, 356, 1.

<sup>3</sup> Wallach and Walker, *Annalen*, 1892, 271, 283.

<sup>4</sup> Henderson, McCrone, and Robertson, *J.*, 1929, 1368.

<sup>5</sup> Deussen, *Annalen*, 1912, 388, 157; *J. pr. Chem.*, 1914, [2], 90, 325.

formed by the attachment of  $N_2O_3$  to one double bond; and it takes up a molecule of halogen acid, which establishes the presence of a second double bond.<sup>1</sup> The fact that  $\gamma$ -caryophyllene contains two double bonds is proved by its forming a bishydrochloride.<sup>2</sup> In the cases of clovene and isoclovene, the necessary evidence is furnished by refractive index measurements.<sup>3</sup> The molecular refractions of the various  $C_{15}H_{24}$  types, calculated from the usual formula, are as follows:—

Openchain compound with 4 double bonds					$[R_L]_D = 69.60$
Monocyclic	"	"	3	"	$[R_L]_D = 67.87$
Dicyclic	"	"	2	"	$[R_L]_D = 66.13$
Tricyclic	"	"	1	"	$[R_L]_D = 64.40$
Tetracyclic	"	"	0	"	$[R_L]_D = 62.66$

The experimental value for clovene is  $[R_L]_D = 64.1$ , and for isoclovene it is  $[R_L]_D = 64.11$ , both values being close to the 64.40 required for a tricyclic substance.

## 2. The Degradation Products of the Caryophyllenes

Numerous decomposition products of the caryophyllenes have been isolated and examined. Interesting constitutional results have been obtained from investigations of the products of oxidation. The scheme on p. 165 shows some of the substances isolated and makes their relationships clearer.

$\beta$ - and  $\gamma$ -caryophyllene fractions yield the same dihydrochloride and it is probable that the two hydrocarbons differ only in the position of one double bond. Further evidence shows

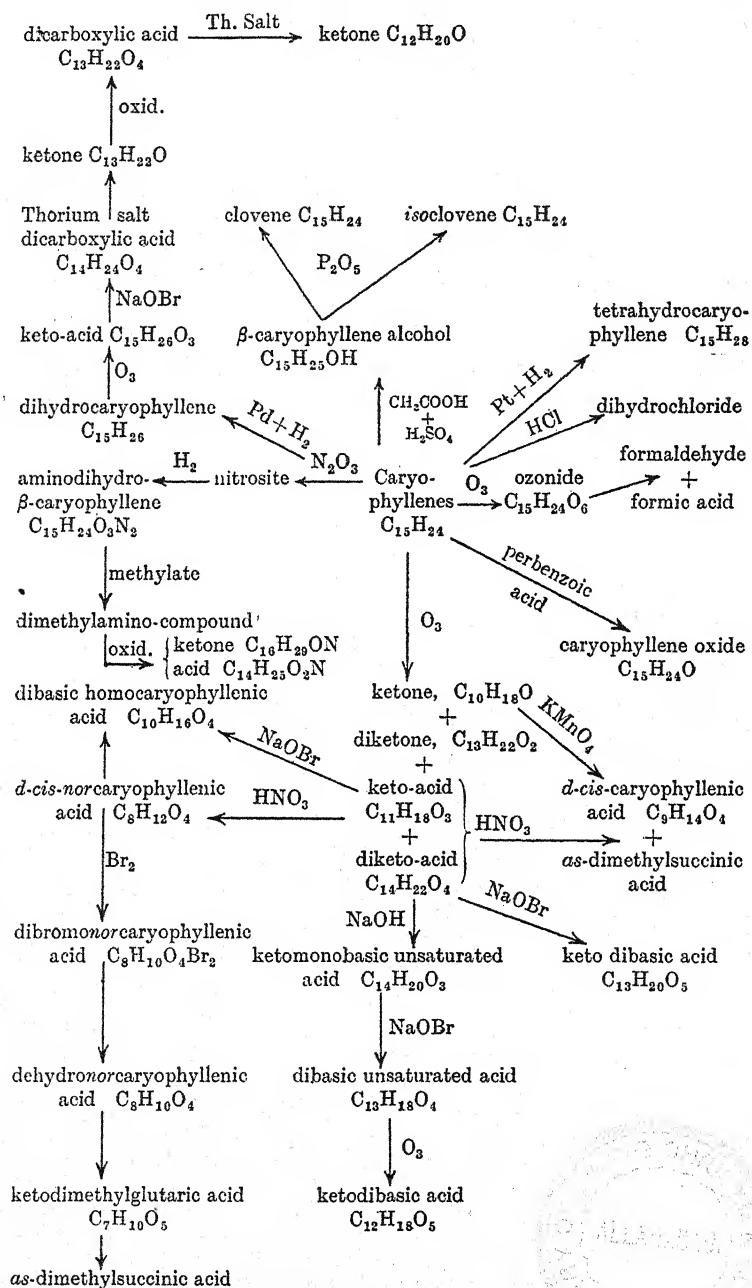
the presence of the isopropenyl,  $-C \begin{smallmatrix} \diagup CH_2 \\ \diagdown CH_3 \end{smallmatrix}$ , skeleton in the molecular structure of  $\beta$ -caryophyllene; the isopropylidene,  $=C \begin{smallmatrix} \diagup CH_3 \\ \diagdown CH_3 \end{smallmatrix}$ , arrangement is assigned to  $\gamma$ -caryophyllene.

Ozonization of the caryophyllene mixture yields four principal products, a keto-acid,  $C_{11}H_{18}O_3$ , a diketo-acid,  $C_{14}H_{22}O_4$ , a ketone,  $C_{10}H_{16}O$  and a diketone,  $C_{13}H_{20}O_2$ . Considerable work has been done on the two acidic products and structures have

<sup>1</sup> Deussen, *Annalen*, 1912 388, 157; *J. pr. Chem.*, 1914, [2], 90, 325.

<sup>2</sup> Deussen, *Annalen*, 1907, 356, 20; 1908, 359, 251; 1912, 388, 154.

<sup>3</sup> Henderson, McCrone, and Robertson. *J.*, 1929, 1368.





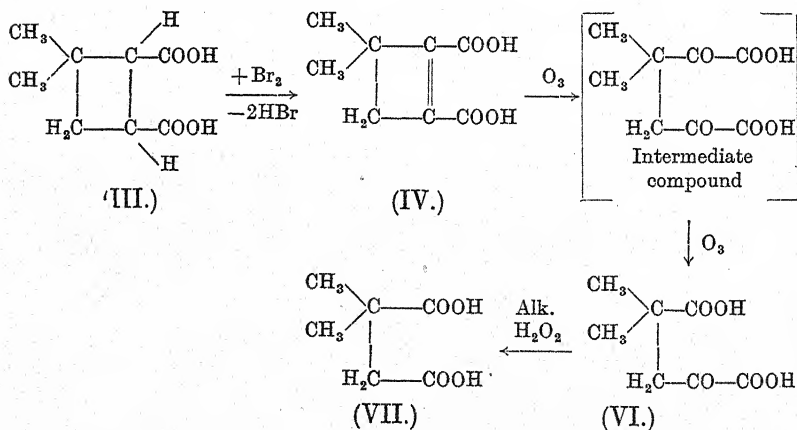
been assigned to them and to  $\beta$ -caryophyllene. On the other hand the two ketones have not received much experimental attention. It will be convenient to deal with each keto-acid and its derivatives separately.

### 3. The Keto-acid, $C_{11}H_{18}O_3$

This acid when oxidized with nitric acid yields the dibasic caryophyllenic acid,  $C_9H_{14}O_4$ , and *as*-dimethylsuccinic acid. The detection of the succinic acid derivative proves the presence

of the grouping  $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CH}_3 \end{array}$  in the caryophyllene system. In

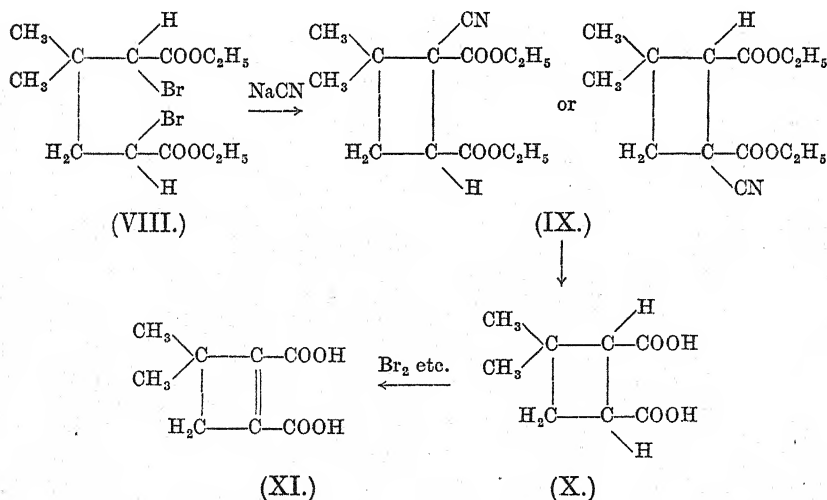
addition, oxidation in this way, or by permanganate followed by nitric acid yields *d*-*cis*-*nor*caryophyllenic acid,  $C_8H_{12}O_4$ , which can be converted through the dibromo-compound into dehydro-*nor*caryophyllenic acid,  $C_8H_{10}O_4$  (IV.). This dibasic acid is unsaturated and on oxidation yields first  $\alpha'$ -keto- $\alpha\alpha$ -dimethylglutaric acid (VI.) and finally *as*-dimethylsuccinic acid (VII.) The simplest explanation of these latter changes is that the dehydro-acid (IV.) is 3 : 3-dimethyl- $\Delta^1$ -cyclobutene-1 : 2-dicarboxylic acid, and that *d*-*cis*-*nor*caryophyllenic acid (III.) is *d*-*cis*-3 : 3-dimethylcyclobutane-1 : 2-dicarboxylic acid.<sup>1</sup> The structures are given below.



<sup>1</sup> Ramage and Simonsen, *J.*, 1934, 1806 ; 1935, 532.

These conclusions have been confirmed by the syntheses of *cis*- and *trans*-*dl*-*nor*caryophyllenic acids and dehydro-*nor*caryophyllenic acid.<sup>1</sup> Ethyl  $\alpha\alpha'$ -dibromo- $\beta\beta$ -dimethyladipate (VIII.) was refluxed with sodium cyanide in ethyl alcohol to effect ring formation. The cyano-ester (IX.) obtained was heated with hydrochloric acid to hydrolyse and decarboxylate it. Further heating with acid under pressure yielded *dl*-*trans*-3 : 3-dimethyl cyclobutane-1 : 2-dicarboxylic acid (X.) identical with *nor*caryophyllenic acid from natural sources. The *dl*-*cis*-acid was obtained through the *dl*-*trans*-anhydride.

The *dl*-*trans*-acid was treated with phosphorus pentachloride and then with bromine. The bromo-compound was esterified with methyl alcohol and then converted into 3 : 3-dimethyl- $\Delta^1$ -cyclobutene-1 : 2-dicarboxylic acid (XI.) by the action of alcoholic potassium hydroxide followed by concentrated hydrochloric acid. This unsaturated acid was found to be the same as dehydro-*nor*caryophyllenic acid derived from natural caryophyllene. The following represents the steps in the syntheses :

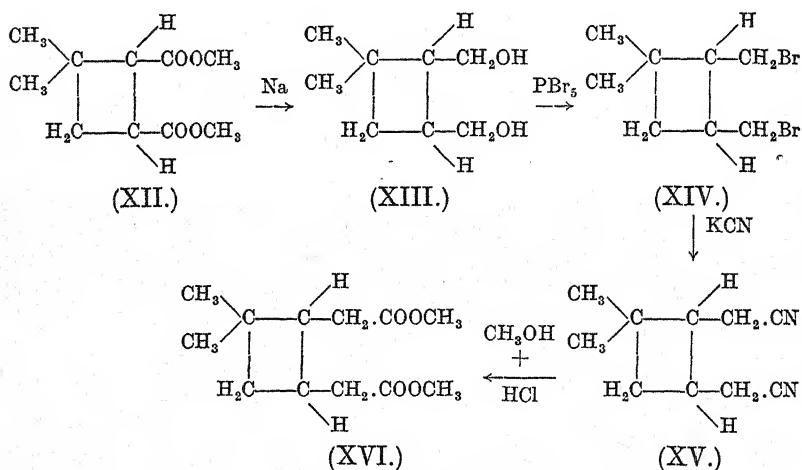


It is obvious that the synthesis of *nor*caryophyllenic acid establishes beyond any doubt the presence of the dimethyl-cyclobutane ring in the caryophyllene structure.

<sup>1</sup> Rydon, J., 1936, 593.

The relationship between *nor*caryophyllenic acid and homocaryophyllenic acid has been established in the following way.<sup>1</sup>

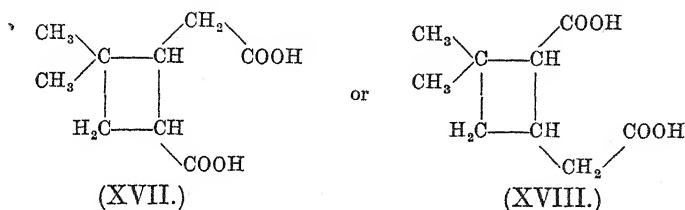
The methyl-ester of *d*-*cis*-*nor*caryophyllenic acid (XII.) was reduced to the glycol (XIII.), from which the dibromo-compound (XIV.) was prepared. The dibromo-compound was converted into the dinitrile (XV.) and finally hydrolysed in the presence of methyl alcohol to the ester of homocaryophyllenic acid (XVI.). From a comparison of their dianilides it is thought probable that this synthetic homocaryophyllenic acid and the homo-acid obtained by the action of ozone and sodium hypobromite on caryophyllene are identical.



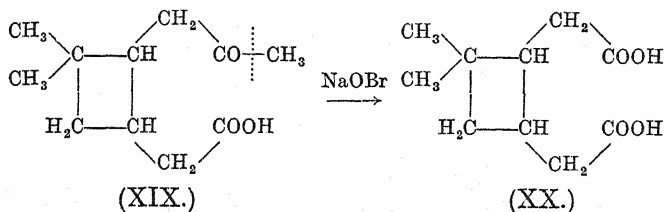
The relationship between *d*-*cis*-caryophyllenic acid and *d*-*cis*-*nor*caryophyllenic acid has also been established.<sup>2</sup> Caryophyllenic acid was converted into bromocaryophyllenic acid and treated with silver oxide in aqueous solution. The hydroxy acid formed was oxidized successively with lead peroxide and potassium permanganate, yielding *d*-*cis*-*nor*caryophyllenic acid. It follows that caryophyllenic acid must have one of the two structures, (XVII.) or (XVIII.).

<sup>1</sup> Ramage and Simonsen, *J.*, 1937, 73.

<sup>2</sup> Ramage and Simonsen, *J.*, 1935, 532.



With this information regarding the structures of caryophyllenic and homocaryophyllenic acids it is now possible to give a structure to the more complex keto-acid,  $C_{11}H_{18}O_3$  (XIX.), obtained directly from caryophyllene by ozonolysis. The keto-acid yields homocaryophyllenic acid (XX.) on treatment with sodium hypobromite. This change may be represented as follows:—

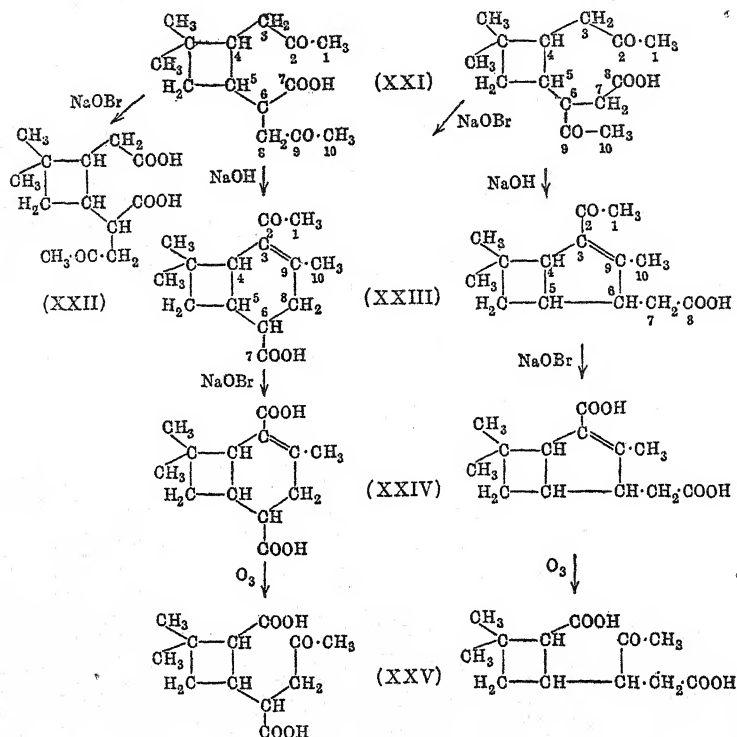


#### 4. The Diketo-acid, $C_{14}H_{22}O_4$

This diketo-acid when oxidized with nitric acid yields caryophyllenic acid and *as*-dimethylsuccinic acid, giving an indication of the structural framework of the compound. The action of sodium hypobromite on the diketo-acid (XXI.) produces a keto-dibasic acid,  $C_{13}H_{20}O_5$  (XXII.), whilst the action of sodium hydroxide solution yields an unsaturated keto-acid,  $C_{14}H_{20}O_3$  (XXIII.), presumably by ring closure at the carbon atoms marked 3 and 9. Sodium hypobromite converts this substance into an unsaturated dibasic acid,  $C_{13}H_{18}O_4$  (XXIV.), and finally ozonization yields a keto-dibasic acid,  $C_{12}H_{18}O_5$  (XXV.).<sup>1</sup> These changes may be explained in two ways: by representing the diketo-acid as a derivative of caryophyllene containing either a six-membered ring or a seven-membered ring in the molecule.<sup>2</sup>

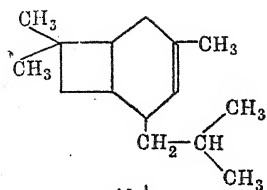
<sup>1</sup> Ruzicka and Wind, *Helv. Chim. Acta*, 1931, 14, 410; Ruzicka, Zimmermann, and Huber, *ibid.*, 1936, 19, 343.

<sup>2</sup> Rydon, *Chem. and Ind.*, 1938, 123.



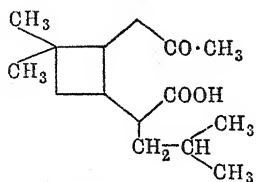
Further evidence supports the proposal that at least one isomer of the caryophyllene mixture has a seven-membered ring structure. Technical caryophyllene was given a preliminary purification and catalytically reduced to dihydrocaryophyllene (XXVI.). Oxidation of this compound yielded an acid,  $\text{C}_{15}\text{H}_{26}\text{O}_3$  (XXVII.), which by the action of sodium hypobromite was converted into a dibasic acid,  $\text{C}_{14}\text{H}_{24}\text{O}_4$  (XXVIII.). The thorium salt of this acid was heated under reduced pressure to convert it into the ketone,  $\text{C}_{13}\text{H}_{22}\text{O}$  (XXIX.). The oxymethylene derivative of the ketone was ozonized, yielding the dicarboxylic acid,  $\text{C}_{13}\text{H}_{22}\text{O}_4$  (XXX.). The thorium salt of this acid yielded a small quantity of the ketone,  $\text{C}_{12}\text{H}_{20}\text{O}$  (XXXI.).<sup>1</sup> These steps are shown below for both a six-membered and a seven-membered ring caryophyllene:

<sup>1</sup> Ruzicka et al., *Helv. Chim. Acta*, 1939, 22, 716.



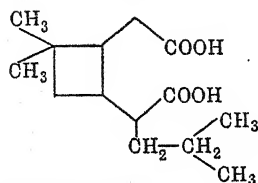
(XXVI)

oxid  
↓



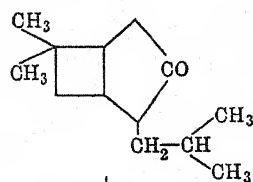
$C_{15}H_{26}O_3$   
(XXVII)

NaOBr  
↓



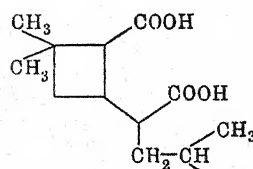
$C_{14}H_{24}O_4$   
(XXVIII)

Heat Th salt  
↓



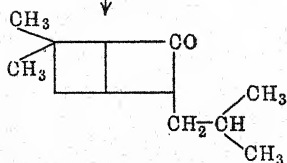
$C_{13}H_{22}O$   
(XXIX)

↓

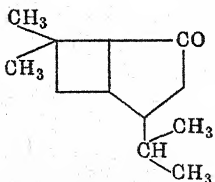
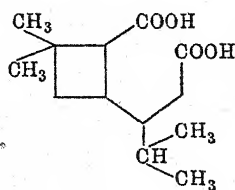
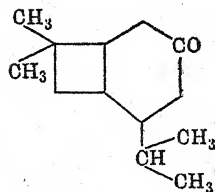
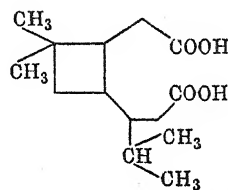
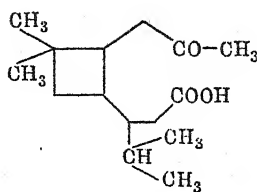
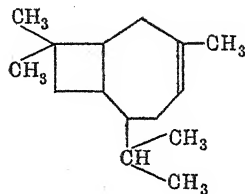


$C_{13}H_{22}O_4$   
(XXX)

Heat  
↓ Th salt



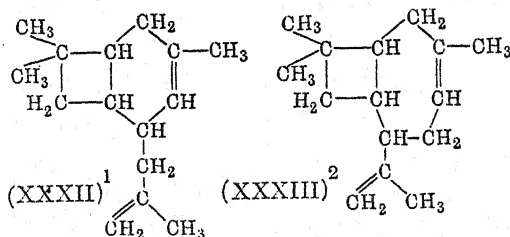
$C_{12}H_{20}O$   
(XXXI)



Inspection of these formulæ show that the dicarboxylic acid,  $C_{13}H_{22}O_4$  (XXX.) derived from a six-membered ring caryophyllene is a glutaric acid derivative, whilst a seven-membered ring caryophyllene produces a substituted adipic acid. Glutaric acid and its derivatives cannot be cyclized to ketones through their salts. On the other hand adipic acids give moderate yields of the cyclic derivatives. From these results, therefore it is probable that one constituent at least of the caryophyllene mixture should be formulated as a seven-membered ring compound.

### 5. The Structure of $\beta$ -Caryophyllene

From consideration of the foregoing experimental facts and an inspection of the diagrams of the degradation products of caryophyllene it is clear that more evidence must be obtained before "finis" can be written to the constitutional history of the caryophyllenes. To sum up, two structures for  $\beta$ -caryophyllene, the principal constituent of the caryophyllene mixture, have been put forward. Each structure accounts satisfactorily for the formation of some of the derivatives obtained. The two formulæ are (XXXII.) and (XXXIII.).\*



Formula (XXXII.) explains the formation of the keto-acid,  $C_{11}H_{18}O_3$  and of the diketo-acid,  $C_{14}H_{22}O_4$ . Difficulties are, however, met when attempts are made to account for the isomerization of caryophyllene to clovene. Similarly the ketone,  $C_{10}H_{18}O$  and the diketone,  $C_{13}H_{22}O_2$  obtained by ozonolysis cannot be satisfactorily derived from this structure.

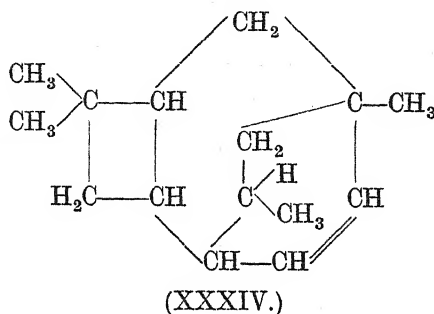
\* See section on Azulenes.

<sup>1</sup> Ruzicka, *Chem. and Ind.*, 1935, 54, 509; Ruzicka, Zimmermann, and Huber, *loc. cit.*

<sup>2</sup> Rydon, *Chem. and Ind.*, 1938, 57, 123.



Formula (XXXIII.) containing a seven-membered ring accounts for the diketo-acid,  $C_{14}H_{22}O_4$ . It also permits a ready explanation to be made of the transformation into clovene, Clovene on this basis becomes (XXXIV.).



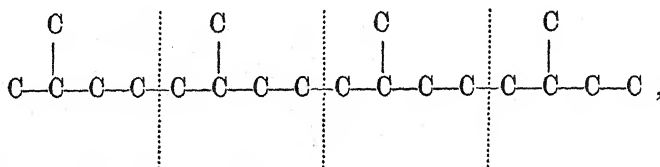
The keto-acid,  $C_{11}H_{18}O_3$  and its derivatives, however, do not fall into place in this scheme. The difficulties encountered in the investigations of the caryophyllenes require no emphasis here; magnificent work has been done and many difficulties overcome. The research work now being pursued on the numerous outstanding constitutional problems will no doubt be carried to a successful conclusion.

## CHAPTER VI

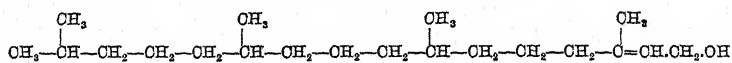
### THE DITERPENE GROUP OF COMPOUNDS

#### A.—INTRODUCTORY

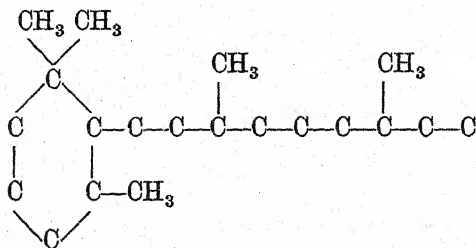
A DITERPENE compound with twenty carbon atoms in its molecular framework may be regarded as built up of four isopentane fragments,



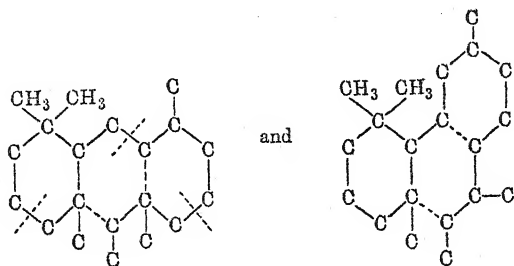
from which a number of different molecular forms may arise. Some of these forms are known amongst natural products. For instance, the bixin molecule has an open chain structure containing this grouping, and the accepted structure for phytol, which forms part of the chlorophyll molecule is



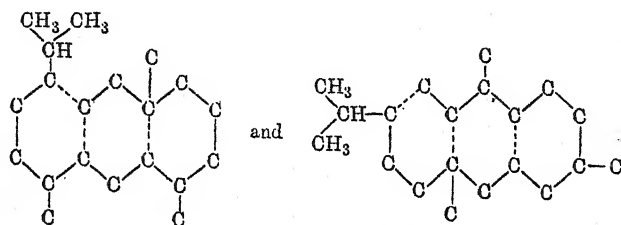
Where cyclization of part of the chain has taken place the vitamin A skeleton results,



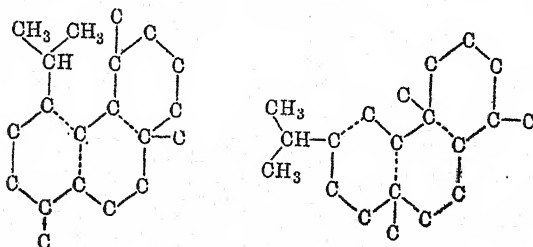
Complete cyclization may lead to compounds of the anthracene and phenanthrene types. A vitamin A type of compound could on further ring formation pass into the forms



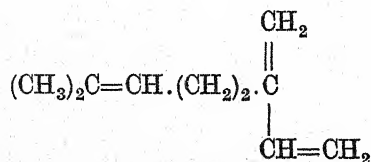
On the other hand, when the isopropyl group appears as a side chain, the structures for anthracene derivatives could be



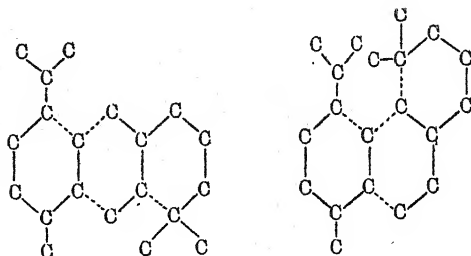
and for phenanthrene formations



There is a further theoretical possibility that the diterpene structure could be formed by the dimerisation of two monoterpene residues giving rise to open-chain and cyclic forms. For example, myrcene has the structure



and two such residues could cyclize to anthracene and phenanthrene derivatives not identical with those from four isopentane units joined "head to tail."



And finally, the isoprene groups may have an irregular arrangement in the molecular structure as appears to be the case in abietic and pimaric acids.

#### B.—THE CAMPHORENES

When oil of camphor is distilled under reduced pressure, the fraction which comes over at 180°–190° C. under 11 mm. pressure is separable into two hydrocarbons<sup>1</sup> having the molecular weight corresponding to  $C_{20}H_{32}$ . One of these substances— $\alpha$ -camphorene—is distinguished by the fact that it yields a tetrahydrochloride,  $C_{20}H_{36}Cl_4$ , when it is treated with hydrogen chloride.

The hydrocarbon regenerated from this tetrahydrochloride had a molecular refraction of 90.6, which is very close to the value (90.49) calculated for a molecule containing four ethylenic linkages. This is confirmed by the fact that on catalytic reduction<sup>2</sup> the hydrocarbon takes up eight hydrogen atoms and forms an octahydride,  $C_{20}H_{40}$ .

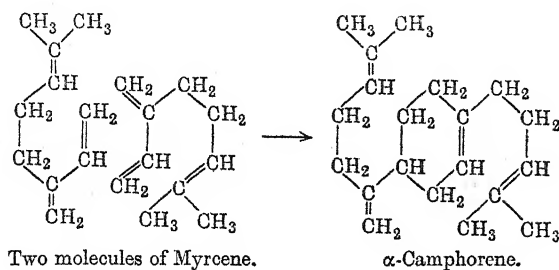
Of especial interest is the fact that  $\alpha$ -camphorene has been detected among the dimyrcenes which are formed<sup>3</sup> when myrcene is heated for several hours in a sealed tube at 250°–260° C. This reaction not only indicates a genetic relationship between myrcene and  $\alpha$ -camphorene but also represents a direct synthesis of the higher terpene from the lower one. This myrcene di-

<sup>1</sup> Semmler and Rosenberg, *Ber.*, 1913, 46, 771.

<sup>2</sup> Semmler and Jonas, *Ber.*, 1914, 47, 2077.

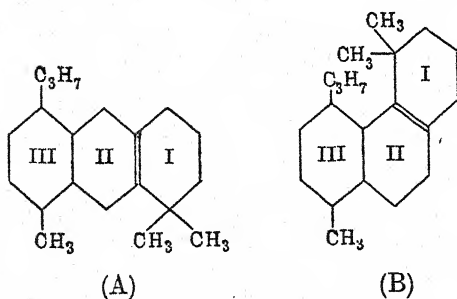
<sup>3</sup> *Ibid.*, 1913, 46, 1566.

merization is formulated by Ruzicka and Stoll<sup>1</sup> in the following way:—



Ruzicka and Stoll found that boiling with 95 per cent. formic acid converts  $\alpha$ -camphorene into a bicyclic diterpene, whilst further treatment results in the formation of a tricyclic diterpene. These two ring-closures are paralleled by analogous cyclizations in the olefinic terpene group.\*

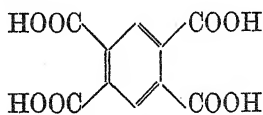
If the cyclization occurs with the two side-chains in the positions shown in the formulæ, the ring-closure should produce an anthracene derivative having the structure shown in (A). On the other hand, if one of the side-chains swings round through  $180^\circ$  about an axis passing through the 1:4-positions of the central ring in the  $\alpha$ -camphorene formula, subsequent cyclization should yield a phenanthrene derivative with the structure shown in (B).



<sup>1</sup> Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, 7, 271.

\* In this connection it may be mentioned that  $\alpha$ -camphorene can be obtained from linalool by heating the terpene alcohol in a sealed tube with anhydrous oxalic acid.

Now when the tricyclic hydrocarbon is oxidized with sulphuric acid and manganese dioxide, pyromellitic acid is one of the degradation products :—



Pyromellitic acid.

This acid could obviously be produced from the central portion (II.) of Formula (A); whereas a compound of the structure shown in Formula (B) might yield pyrogallallic acid from ring (I.) or prehnitic acid from ring (II.) or ring (III.,) but no pyromellitic acid could be obtained from it.

The tricyclic hydrocarbon must therefore have the structure (A); and from this it follows that  $\alpha$ -camphorene is represented by the formula given above. Further evidence in favour of this formula is found when  $\alpha$ -camphorene is reduced to the octahydro-derivative,  $C_{20}H_{40}$ , and this derivative is oxidized with manganese dioxide and sulphuric acid. Some terephthalic acid is thus obtained, which obviously results from conversion of the central ring of  $\alpha$ -camphorene into a benzene nucleus and a subsequent oxidation of the two para side-chains to carboxyls.

Less is known about the second constituent of the high-boiling fraction of camphor oil. When the oil is treated with hydrogen chloride to produce the tetrahydrochloride of  $\alpha$ -camphorene, an oily residue remains which, on boiling with alcoholic potash, yields  $\beta$ -camphorene. Its molecular refraction is 88.61, which suggests that it may be bicyclic in structure.

## C.—ABIETIC ACID

### 1. General

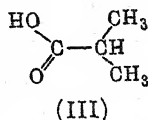
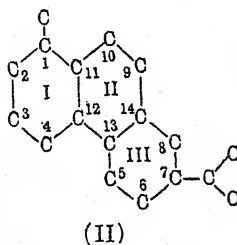
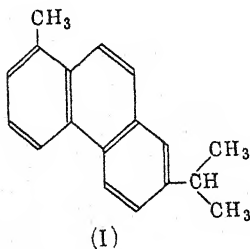
The crude oleoresin obtained from trees of the species *Pinus* is a mixture of essential oils and acidic resins. The essential oils may be removed by steam distillation. The solid residue known as colophony or rosin on further treatment either by distillation or extraction by solvents yields abietic acids as the principal products. Abietic acid is not a primary constituent of the parent oleoresin, but is regarded as an isomerization product of the original unstable heat- and acid-sensitive oleoresin acids.

## 2. The Molecular Framework of Abietic Acid

Abietic acid has the molecular formula,  $C_{20}H_{30}O_2$ . It contains a carboxyl group, and on dehydrogenation with sulphur or selenium is converted into retene (1-methyl-7-isopropyl-phenanthrene) (I.).<sup>1</sup> This establishes the structure of the major portion of the abietic acid molecule. During the fusion with sulphur or selenium two carbon atoms are eliminated from the molecule, and it is inferred that in addition to the carboxyl group an angle methyl group is present in the acid. It is not to be concluded, however, that the carboxyl group also occupies an angle position. The conditions of fusion are severe and carboxyl may be eliminated from any position in the ring system. There are four angle positions in the abietic framework, namely, at carbon atoms numbered 11, 12, 13, and 14 (see II. below).

## 3. The Ethylenic Linkages of Abietic Acid

Abietic acid may be reduced by steps to give first dihydroabietic acid and then tetrahydroabietic acid.<sup>2</sup> Similarly by steps of mild oxidation dihydroxy- and tetrahydroxyabietic acids may be isolated.<sup>3</sup> Abietic acid, therefore, contains two ethylenic bonds. When abietic acid is oxidized isobutyric acid (III.) is one of the products. This points to position 6-7 or 7-8 of ring III for one of the bonds.



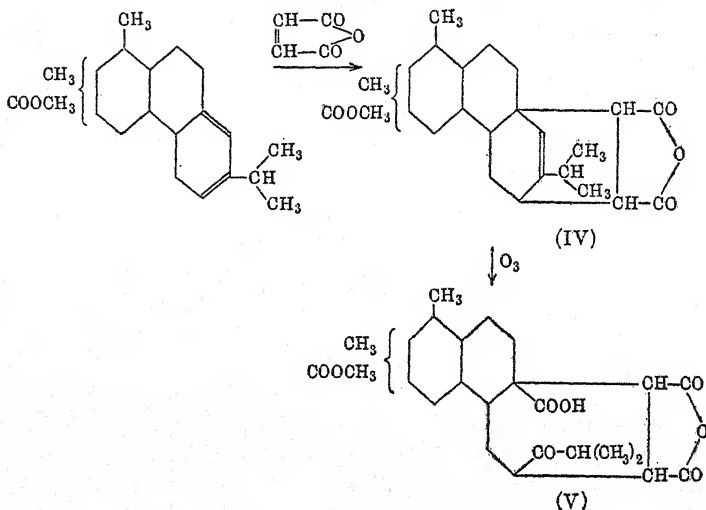
<sup>1</sup> Vesterberg, *Ber.*, 1903, 36, 4200; Ruzicka and Waldmann, *Helv. Chim. Acta*, 1933, 16, 842.

<sup>2</sup> Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, 5, 315.

<sup>3</sup> Levy, *Ber.*, 1909, 42, 4305; 1926, 59, 1302; 1928, 61, 616; Ruzicka and Meyer, *Helv. Chim. Acta*, 1932, 6, 1097.



It was considered that the double carbon bonds were conjugated as methyl abietate yields an additive compound (IV.) with maleic anhydride, which could be oxidized by ozone to a keto-acid,  $C_{25}H_{34}O_8$ , with the possible structure (V.).<sup>1</sup> These reactions could be explained by placing the double bonds at positions 6-7 and 8-9.



The evidence of spectroscopic and refractivity measurements on abietic acid and the ethyl ester, however, could not be reconciled with such a system of unsaturation.

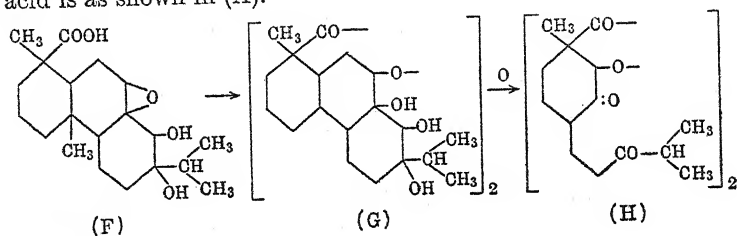
By comparison with *l*-pimaric acid (see p. 189) it is thought that the double bonds of abietic acid may be in the positions 7-8 and 14-9, and certain chemical evidence points in this direction. When tetrahydroxyabietic acid (C) was treated with lead tetracetate an indefinite substance (D) ( $C_{20}H_{30}O_6$  or  $C_{20}H_{28}O_5$ ) was produced, which with sodium hypobromite yielded a tetracarboxylic acid,  $C_{15}H_{22}O_8$  (E).<sup>2</sup> These changes may be formulated in the two ways shown below. Two possible structures for abietic acid (A and B) are included for reference.

<sup>1</sup> Ruzicka, Ankersmit, and Frank, *Helv. Chim. Acta*, 1932, 15, 1289; Ruzicka *et al.*, *ibid.*, 1933, 16, 169.

<sup>2</sup> Ruzicka *et al.*, *Helv. Chim. Acta*, 1938, 21, 565.

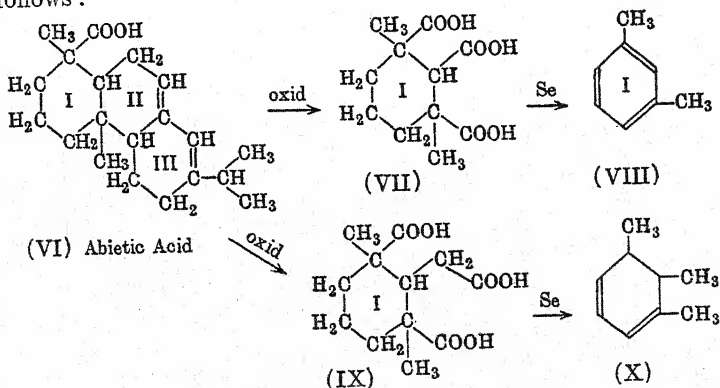


hydroxyl group of another. Oxidation of the ester gave rise to a diketo-inner ester (H). The formation of a diketo-compound with the loss of one carbon atom from each abietic acid residue shows that the compound (G) contains a glycerol grouping in each residue, and consequently proves that in tetrahydro-abietic acid (C) the four hydroxyl groups are attached to adjacent carbon atoms. This can only be so if the structure of abietic acid is as shown in (A).<sup>1</sup>



#### 4. The Angle Methyl Group

When abietic acid (VI.) is oxidized with potassium permanganate or ozone to break up the three-ring system, two of the products are a dimethylcyclohexane tricarboxylic acid,  $C_{11}H_{16}O_6$  (VII.) and a dicarboxylicdimethylcyclohexane acetic acid,  $C_{12}H_{16}O_6$  (IX.). These two acids yield *m*-xylene (VIII.) and 1 : 2 : 3-trimethylbenzene (X.) respectively on dehydrogenation with selenium.<sup>2</sup> These changes may be represented as follows :—



<sup>1</sup> Ruzicka and Sternbach, *Helv. Chim. Acta*, 1941, 24, 223, 504.

<sup>2</sup> Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, 1925, 8, 637; Ruzicka et al., *ibid.*, 1931, 14, 545.

The two acids,  $C_{11}H_{16}O_6$  and  $C_{12}H_{18}O_6$  must be derived from ring I. of the abietic acid system. Ring III. is unsaturated and would be expected to break up under the conditions of oxidation, and Ring II. could not give rise to two methyl groups by oxidation. The formation of *m*-xylene and 1 : 2 : 3-trimethylbenzene clearly points to the two methyl groups occupying 1 : 3 positions relative to one another in abietic acid. The angle methyl group, therefore, must be placed at position 12.

### 5. The Position of the Carboxyl Group

The acid  $C_{11}H_{16}O_6$  when treated with concentrated sulphuric acid at 100–140° C. yields two molecular proportions of carbon monoxide, and abietic acid itself gives carbon monoxide at 50–60° C. These decompositions point to carboxyl attached to a tertiary carbon atom.<sup>1</sup> A carboxyl group attached to a secondary carbon atom is generally much more stable towards sulphuric acid.

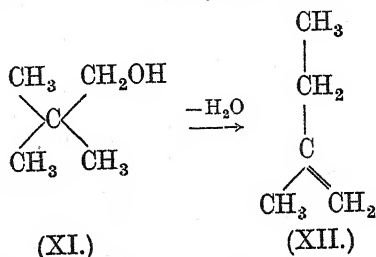
The concluding evidence leaves no doubt that the carboxyl group is attached at position 1 in ring I. along with a methyl group.

When methyl abietate (XIII.) is reduced with sodium and alcohol, the alcohol abietinol,  $C_{20}H_{32}O$  (XIV.) is formed, which by the action of phosphorus pentachloride or naphthalene-2-sulphonic acid yields the compound known as "methylabietin,"  $C_{20}H_{30}$  (XV.). Dehydrogenation of "methylabietin" with sulphur gives rise to homoretene (XVI.).<sup>2</sup> Homoretene on oxidation yields phenanthrene-1 : 7-dicarboxylic acid and has been shown by its synthesis to be 1-ethyl-7-isopropylphenanthrene.<sup>2</sup> The obvious explanation of these changes is that the carboxyl group of abietic acid is not directly attached to ring I., but forms the end of a two-carbon side-chain,  $R-CH_2-COOH$ , which is reduced first to the alcohol abietinol,  $R-CH_2-CH_2OH$ , and finally to the hydrocarbon homoretene,  $R-CH_2CH_3$ . Oxidation of homoretene would then lead to phenanthrene-1 : 7-dicarboxylic acid by degradation of the side-chains. The presence of this two-carbon side-chain in abietic acid would, however, be an exception to the well-established "isoprene" rule, and further, abietic acid can only be esterified with difficulty, whereas an acid of the type mentioned above would be expected to esterify with comparative ease. An alternative arrangement of the carboxyl group in abietic acid must therefore be sought.

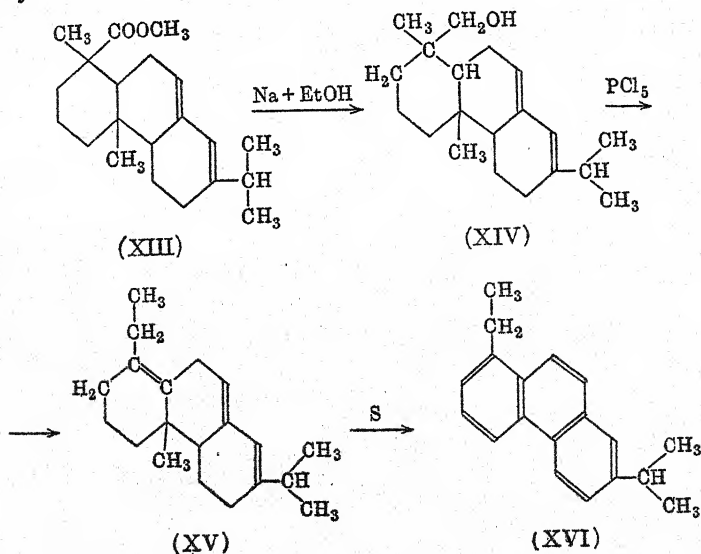
<sup>1</sup> Vocke, *Ber.*, 1932, 497, 247.

<sup>2</sup> Haworth, *J.*, 1932, 2717.

The carboxyl group is placed at position 1 in ring I. along with the methyl group and it is considered that a migration of a carbon atom occurs during the dehydration of abietinol by phosphorus pentachloride. Consequently "methylabietin" (XV.) may be given the structure shown, and on dehydrogenation would yield homoretene. The intramolecular change postulated is of the Wagner-Meerwein type, and may be compared with the change which takes place when *isoborneol* is dehydrated to camphene or when *tertiary* butylcarbinol (XI.) is dehydrated to 1:1-methylethylethylene (XII.).<sup>1</sup>

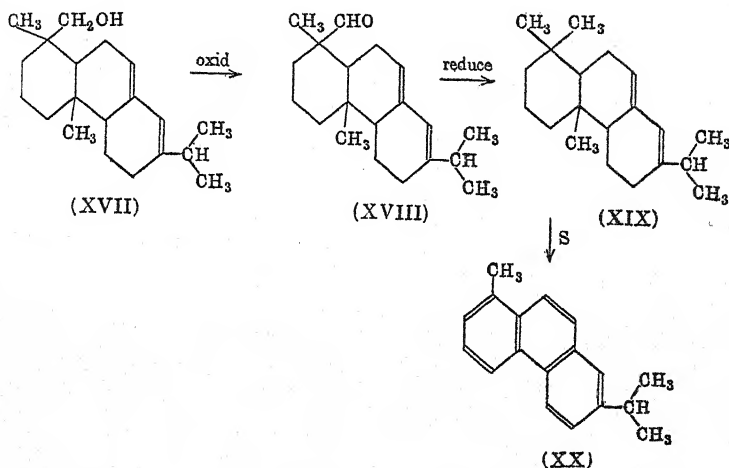


The steps in the conversion of methylabietate into homoretene may be illustrated as follows:—



<sup>1</sup> Ingold, J., 1923, 123, 1706; Whitmore, J. Amer. Chem. Soc., 1932, 54, 3274.

If abietinol (XVII.) is oxidized to the aldehyde, abietinal (XVIII.), and this is followed by reduction, a new "methylabietin" (XIX.) is formed which on dehydrogenation yields retene (XX.).<sup>1</sup> In this series of changes there is no dehydration involving an intramolecular change and consequently the structure of this "methylabietin" (XIX.) should be as shown below. From this compound one of the two tertiary methyl groups would disappear in the dehydrogenation to the aromatic substance, retene (XX.).



The structure of abietic acid may, therefore, be regarded as settled (VI.).

### D.—*d*-PIMARIC ACID

#### 1. General

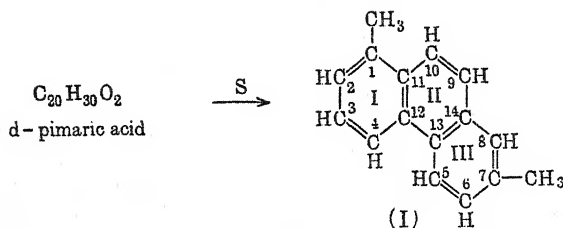
This unsaturated acid is obtained along with *l*-sapietic acid from French colophony, and is isomeric with it. It is more stable than either sapietic acid or abietic acid.

#### 2. The Molecular Framework

Dehydrogenation with sulphur converts pimaric acid into pimanthrene (1:7-dimethylphenanthrene) (I.).<sup>2</sup>

<sup>1</sup> Ruzicka *et al.*, *Helv. Chim. Acta*, 1933, 16, 169.

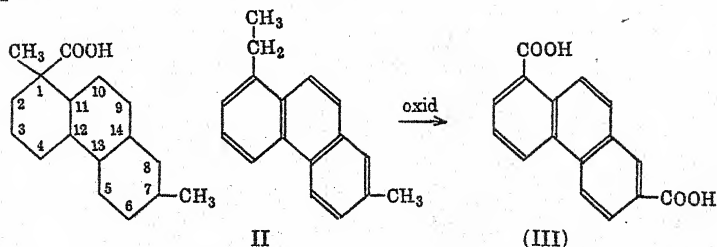
<sup>2</sup> Ruzicka and Balas, *Helv. Chim. Acta*, 1924, 7, 875.



This proves the arrangement of sixteen of the carbon atoms of the molecule.

### 3. The Carboxyl Group

Oxidation of pimmaric acid with an excess of potassium permanganate gives rise to two acids,  $\text{C}_{11}\text{H}_{16}\text{O}_6$  and  $\text{C}_{12}\text{H}_{18}\text{O}_6$  identical with those obtained from abietic acid by similar treatment (see p. 182).<sup>1</sup> These acids can only be derived from ring I. of the pimmaric acid system and consequently the carboxyl group is placed at position 1 in ring I. There is another point of resemblance with abietic acid, which further points to the position occupied by the carboxyl group. When ethyl pimmarate is reduced with sodium and alcohol to the corresponding alcohol, *d*-pimarol,  $\text{C}_{20}\text{H}_{32}\text{O}$ , and this product is dehydrated by the action of phosphorus pentachloride, "methyl pimmarin" is formed. This product on dehydrogenation yields the hydrocarbon homopimarane (II).<sup>2</sup> Homopimarane on oxidation is converted into phenanthrene-1:7-dicarboxylic acid (III).<sup>3</sup> These changes are similar to those undergone by abietic acid when treated in the same way, and it may be concluded that the carboxyl group of pimmaric acid occupies the same position as in abietic acid (see p. 183).



<sup>1</sup> Ruzicka, Meyer, and Pfeiffer, *Helv. Chim. Acta*, 1925, 8, 637.

<sup>2</sup> Ruzicka and Balas, *loc. cit.*

<sup>3</sup> Ruzicka, de Graaff, and Hosking, *Helv. Chim. Acta*, 1931, 14, 233.



#### 4. The Methyl Groups

The formation of 1:7-dimethylphenanthrene on the dehydrogenation of pimanic acid fixes the positions of two methyl groups. The production of *m*-xylene and 1:2:3-trimethylbenzene from the acids  $C_{11}H_{16}O_6$  and  $C_{12}H_{18}O_6$  respectively points to a third methyl group occupying the angle position 12 in the pimanic acid molecule. Eighteen of the twenty carbon atoms of the molecule have thus been assigned to their positions in the skeleton.

#### 5. The Vinyl Group

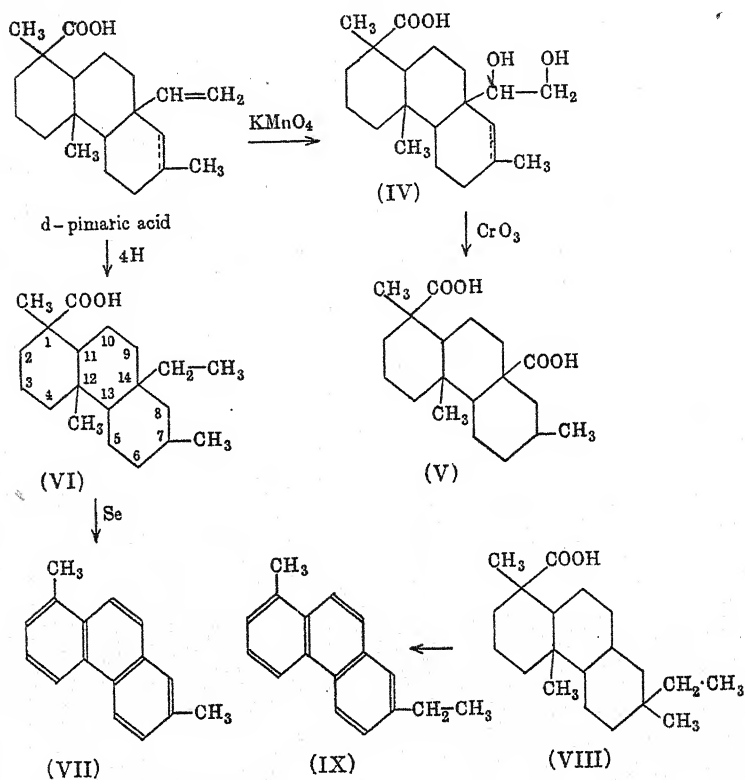
The two remaining carbon atoms are accounted for as follows. Pimanic acid on light ozonization yields some formaldehyde. From this it appears that the molecule contains an unsaturated side-chain containing a terminal methylene group. The two carbon atoms are most probably in the form of a vinyl group  $-CH=CH_2$ .

When pimanic acid is partially oxidized with potassium permanganate it yields a dihydroxyacid (IV.). This acid on further oxidation with chromic acid splits off one carbon atom to yield a dicarboxylic acid,  $C_{19}H_{28}O_4$  (V.).

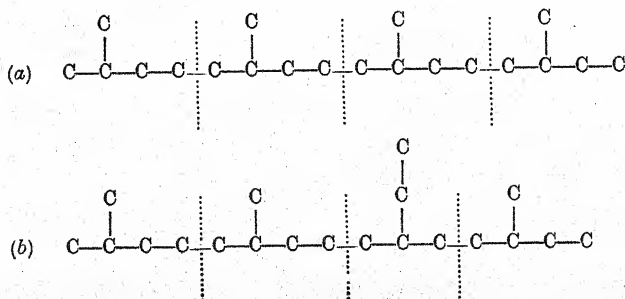
When pimanic acid is converted into tetrahydropimanic acid (VI.) and then dehydrogenated with selenium, it yields pimanthrene (VII.).<sup>1</sup> These results can be adequately explained by placing the side-chain vinyl group at an angle position. Another possible position for the vinyl side-chain is at carbon atom 7 along with the methyl group. A tetrahydropimanic acid (VIII.) of this structure would be expected to yield some 1-methyl-7-ethylphenanthrene (IX.) on dehydrogenation. As none of the ethyl derivative has been detected in the products of reaction, this alternative need not be considered.

There is no evidence that the vinyl group is attached at ring I. This leaves positions 13 and 14. Preference is given to position 14, as this arrangement of the carbon atoms in the molecule can be divided into isoprene groups, whereas the structure with the vinyl group at position 13 cannot be arranged

<sup>1</sup> Ruzicka, de Graaff, Goldberg and Frank, *Helv. Chim. Acta*, 1932, 15, 915.



in this way. It will be noticed, however, that the arrangement of the carbon atoms in the suggested structure for pimaric acid is not a normal head to tail sequence of isoprene units. The arrangements (a) and (b) show the normal head to tail and pimaric acid formations respectively.



## 6. The Ethylenic Linkages

Pimaric acid yields both a dihydro- and a tetrahydro-derivative, but does not form an addition product with maleic anhydride. The acid therefore contains two unconjugated double bonds. The vinyl group has been placed at position 14. This excludes the positions 9-14, 13-14, and 8-14 for the nuclear double bond. The available positions in rings I. and II. are considered unlikely to be unsaturated. The ring double bond is unexpectedly resistant to a number of reagents and at present no definite position in Ring III. can be assigned to it.<sup>1</sup>

E.—*l*-SAPIETIC ACID (*l*-PIMARIC ACID)<sup>2</sup>

Sapietic acid was first isolated from French colophony.<sup>3</sup> It has the same molecular formula,  $C_{20}H_{30}O_2$ , as abietic acid and is considered to be one of the primary acids of oleoresins. In many properties it is closely related to abietic acid; <sup>4</sup> dehydrogenation with sulphur converts sapietic acid into retene, and hot glacial acetic acid readily isomerizes it to abietic acid. The molecular refraction of methyl tetrahydrosapietate agrees with the figure calculated for a tricyclic system. These facts establish the carbon skeleton (I.) of sapietic acid, and the remaining problem is the positions occupied by the double bonds. The acid on catalytic hydrogenation yields a dihydro- and a tetrahydro-compound. Sapietic acid reacts quantitatively with maleic anhydride and with benzoquinone and  $\alpha$ -naphthoquinone at room temperature.<sup>5</sup> Spectroscopic evidence also points to the presence of a conjugated system of two double bonds in the molecule, and in addition it is considered that the bonds are in the same ring.<sup>6</sup> These facts may be summed up in the structure (II.), the double bonds being placed at the positions 7-8 and 13-14.<sup>7</sup>

<sup>1</sup> Ruzicka, Ankersmit, and Frank, *Helv. Chim. Acta*, 1932, 15, 1294; Ruzicka, de Graaff, and Müller, *ibid.*, 1300.

<sup>2</sup> Hasselstrom and Bogert, *J. Amer. Chem. Soc.*, 1935, 57, 2118.

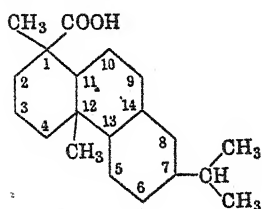
<sup>3</sup> Vesterberg, *Ber.*, 1886, 18, 3331.

<sup>4</sup> Ruzicka, Balas and Vilim, *Helv. Chim. Acta*, 1924, 7, 458.

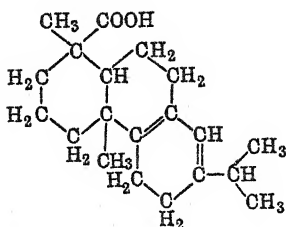
<sup>5</sup> Bacon and Ruzicka, *Chem. and Ind.*, 1936, 55, 546; Wienhaus and Sandermann, *Ber.*, 1936, 69, 2202.

<sup>6</sup> Kraft, *Annalen*, 1935, 520, 133.

<sup>7</sup> Ruzicka, Bacon, and Kuiper, *Helv. Chim. Acta*, 1937, 20, 1542.



(I.)

(II.) *l*-Sapietic Acid

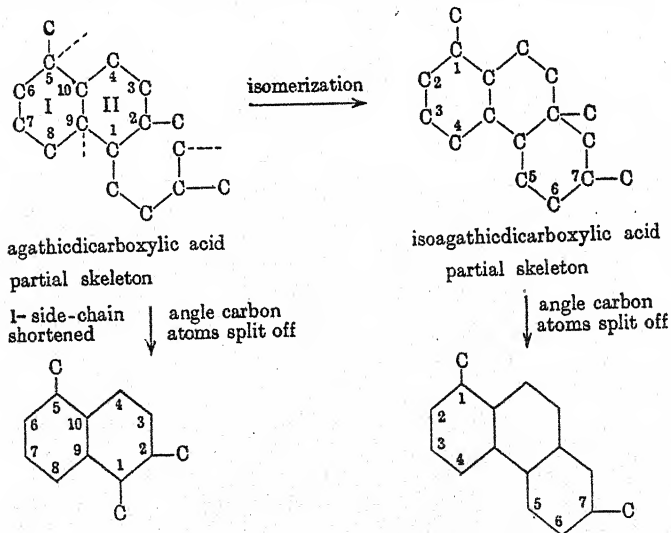
## F.—AGATHIC DICARBOXYLIC ACID

## 1. General

This acid has been isolated in a crystalline condition from kauri and Manila copal resins. It is dibasic and has the molecular formula  $C_{20}H_{30}O_4$ .<sup>1</sup> Various dibasic acids isolated from different copals are probably impure specimens of this acid.

## 2. The Molecular Framework

Agathic dicarboxylic acid by the action of either sulphur or selenium yields 1:2:5-trimethyl-naphthalene. If the acid is first isomerized by means of formic acid to *isoagathic* dicarboxylic



<sup>1</sup> Ruzicka and Hosking, *Annalen*, 1929, 469, 147.

acid and then dehydrogenated the product is pimanthrene (1 : 7-dimethyl-phenanthrene).<sup>1</sup> The formation of the naphthalene derivative in the one case and the phenanthrene compound in the other can be explained by assuming that the isomerization is due to ring formation by a suitable side-chain of agathic dicarboxylic acid as on p. 190. The dicyclic structure of agathic dicarboxylic acid is supported by molecular refractivity measurements.

### 3. The Ethylenic Bonds and the Unsaturated Side-chains

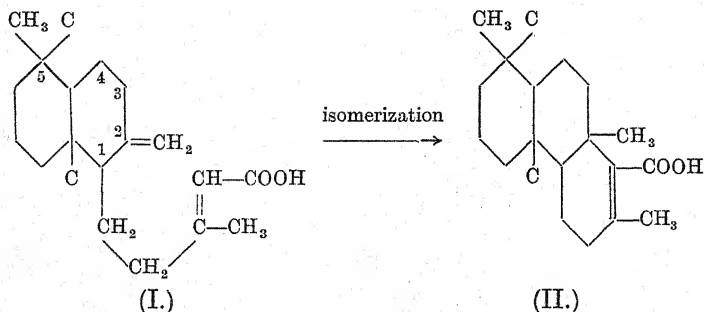
Agathic dicarboxylic acid on catalytic reduction takes up four atoms of hydrogen to yield the saturated tetrahydro-acid. It, therefore, contains two ethylenic bonds, and these, unlike the double bonds of abietic acid or pimaric acid, show no difference in reactivity. By the action of ozone the acid splits off both formaldehyde and oxalic acid. The production of formaldehyde under these conditions points to the presence of a terminal

methylene group  $\text{>C=CH}_2$  in the molecule. The presence of

oxalic acid amongst the products of oxidation indicates that the second double bond also occupies a side-chain position with one

of the carboxyl groups at the end of the chain,  $\text{>C=CH-COOH}$ .

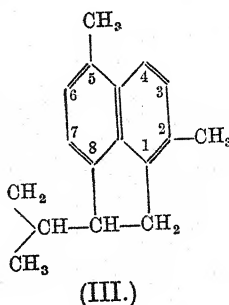
Isoagathic dicarboxylic acid yields on catalytic reduction a dihydro-derivative only and consequently contains one double bond. The isomerization to the tricyclic compound involves, as would be expected, one of the points of unsaturation of agathic dicarboxylic acid.



<sup>1</sup> Ruzicka and Hosking, *Helv. Chim. Acta*, 1930, 13, 1402; 1931, 14, 203.

If the unsaturated side-chains of agathic dicarboxylic acid are placed as shown in structure (I.), the formation of formaldehyde and oxalic acid and the isomerization to the dibasic unsaturated acid (II.) are readily explained.

The point of attachment for the *iso*-hexenyl side-chain at the ring carbon atom 1 is selected, as this arrangement of the twenty carbon atoms is a regular "head to tail" formation of the isoprene units. There is a further indication that the *iso*-hexenyl side-chain occupies position 1 in the ring system. When agathic dicarboxylic acid is dehydrogenated with selenium, in addition to 1:2:5-trimethylnaphthalene, a small amount of another hydrocarbon,  $C_{17}H_{20}$  is formed.<sup>1</sup> The structure of the latter substance is not known with certainty, but from its properties it is thought to contain a naphthalene ring and a third saturated ring. The following structure (III.) appears to be the most appropriate for this compound:—



the third ring being formed from the side-chain at position 1 by coupling up at position 8.

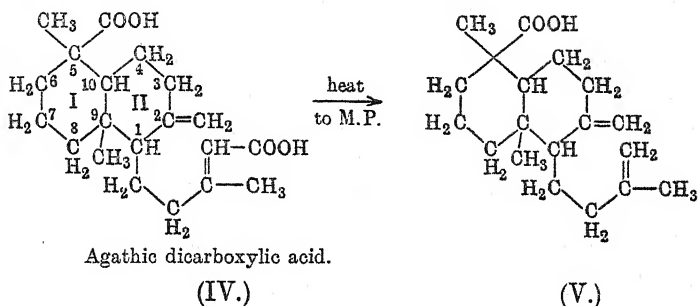
The methylene group of agathic dicarboxylic acid (IV.) is placed at carbon atom 2 in accordance with the evidence of dehydrogenation.

#### 4. The Carboxyl Groups

One carboxyl group has been provisionally placed in the *iso*-hexenyl side-chain with a double carbon bond adjacent. Agathic dicarboxylic acid (IV.) when heated to its melting-

<sup>1</sup> Ruzicka and Hosking, *loc. cit.*

point loses carbon dioxide with the formation of noragathic acid. This behaviour supports the view that one carboxyl group is attached to an unsaturated carbon atom. Noragathic acid contains (V.) two double bonds as it is converted into the tetrahydro-acid by catalytic reduction. The conversion may be formulated as follows :—



Hydrolysis of dimethyl agathate takes place in stages, one ester grouping being readily acted upon, the second only with difficulty. Parallel with this, methyl noragathate also resists hydrolysis. The second carboxyl group of agathic dicarboxylic acid is evidently in a position much more sterically guarded than that of the side-chain carboxyl.

Bearing in mind the isoprene rule, there are two possible positions in ring I. for the second carboxyl group, at carbon atom 5 which carries a methyl group and at the angle carbon atom 9. It was possible to make a choice between these two alternatives in the following way.<sup>1</sup> When *isoagathic* dicarboxylic acid (VI.) was heated one carboxyl group was readily destroyed, the product being *isonoragathic* acid. The methyl ester (VII.) of this new acid was reduced by sodium and ethyl alcohol to *isonoragathenol* (VIII.). Dehydration of the alcohol by heating with naphthalene-2-sulphonic acid under diminished pressure gave a hydrocarbon,  $C_{19}H_{30}$  (IX.), which on dehydrogenation with selenium yielded 7-methyl-1-ethylphenanthrene (X.) These changes are parallel with the conversion of abietic acid into homoretene and of *d*-pimaric acid into homopimanthrene (see pages 184 and 186) and may be formulated as follows.

<sup>1</sup> Ruzicka and Jacobs, *Rec. trav. chim.*, 1938, 57, 509.





(X)

(IX)

of

2012

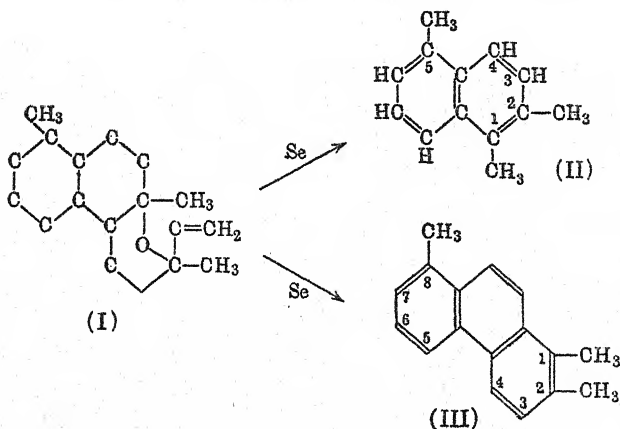
## 1. General

Q70

...and

2. *Manoyl Oxide*

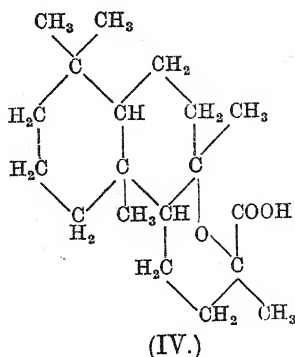
This compound has the molecular formula  $C_{20}H_{34}O$ . It contains one ethylenic bond, as it absorbs one molecule of hydrogen only. It does not answer to any of the usual tests for the hydroxyl or methoxyl group, and from its inertness it is concluded that the oxygen atom is present in the molecule in ether formation.<sup>1</sup> When treated with ozone, and the ozonide decomposed by the action of water, formaldehyde is produced in considerable quantity: this indicates the presence of at least one terminal methylene group.<sup>2</sup> The action of selenium on manoyl oxide produces 1:2:5-trimethylnaphthalene (II.) and 1:2:8-trimethylphenanthrene (III.). The production of the naphthalene derivative points to a relationship between the oxide and agathic dicarboxylic acid, and demonstrates the presence of a dicyclic carbon system in the molecular framework. The simultaneous formation of naphthalene and phenanthrene derivatives may be explained by giving the oxide the following skeleton structure (I.).



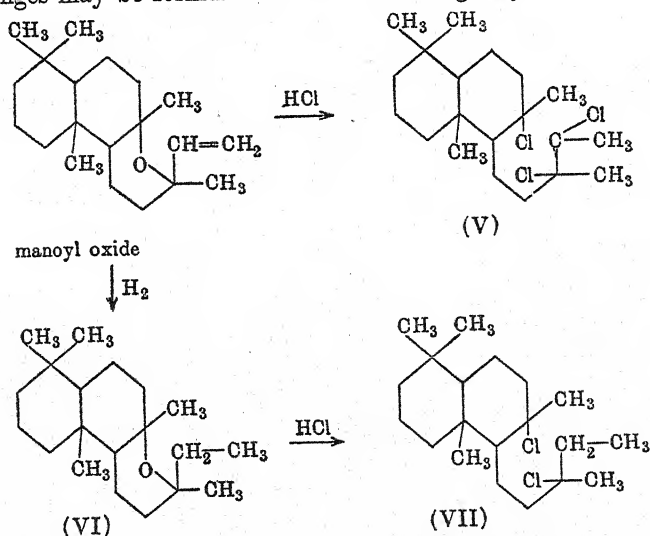
This explanation accounts for eighteen of the twenty carbon atoms in the molecule. This structure has to be confirmed and the two remaining carbon atoms allocated positions in the system. Manoyl oxide can be oxidized by potassium permanganate to a monocarboxylic acid,  $C_{19}H_{32}O_3$  (IV.), in which the oxide ring is still intact. From the relationship between the oxide and agathic dicarboxylic acid, the manoyl oxide acid derivative may provisionally be represented as follows:—

<sup>1</sup> Hosking and Brandt, *Ber.*, 1934, 67, [B], 1173.

<sup>2</sup> Hosking and Brandt, *Ber.*, 1935, 68, [B], 37, 286.



The formation of this acid with the loss of a carbon atom shows that the methylene group is not directly attached to the ring system.<sup>1</sup> The action of hydrogen chloride in ether on manoyl oxide gives rise to manoenne trihydrochloride,  $C_{20}H_{35}Cl_3$  (V.), and dihydromanoyl oxide (VI.) under similar conditions yields dihydromanoeene dihydrochloride,  $C_{20}H_{36}Cl_2$  (VII.). These changes may be formulated in the following way:—

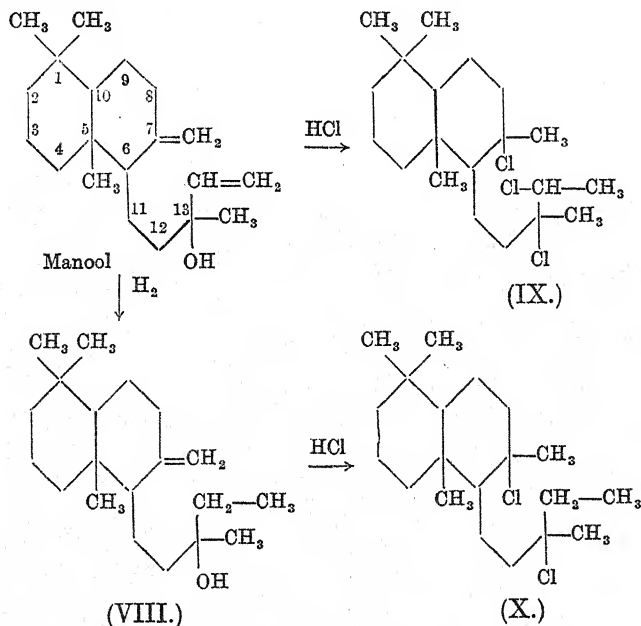


There is no direct evidence that a second methyl group is attached at position 1 in the molecule, and that a methyl group occupies the angle position 5. On account, however, of the close relationship to agathic dicarboxylic acid these positions have been provisionally selected in preference to others in the molecule.

<sup>1</sup> Hosking and Brandt, *New Zealand J. Sci. Tech.*, 1936, 17, 750, 755.

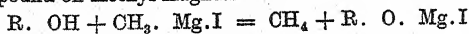
## 3. Manool

Having the molecular formula,  $C_{20}H_{34}O$ , manool is isomeric with manoyl oxide. It is shown by the Zerevitinov reaction\* to contain one hydroxyl group. As it does not react with orthophthalic anhydride it is a tertiary alcohol. When manool is hydrogenated in the presence of platinum black its yields dihydromanool (VIII.), and with platinum dioxide as the catalyst it is converted into tetrahydromanool. Manool, therefore, contains two double carbon bonds. The action of hydrogen chloride on manool produces manocene trihydrochloride (IX.), and when dihydromanool is similarly acted upon it yields dihydromanocene dihydrochloride (X.).<sup>1</sup> These last two changes establish the close relationship to manoyl oxide and may be formulated as shown below.



The position of the hydroxyl group in manool has been confirmed in the following way. Tetrahydromanool (XI.) was converted

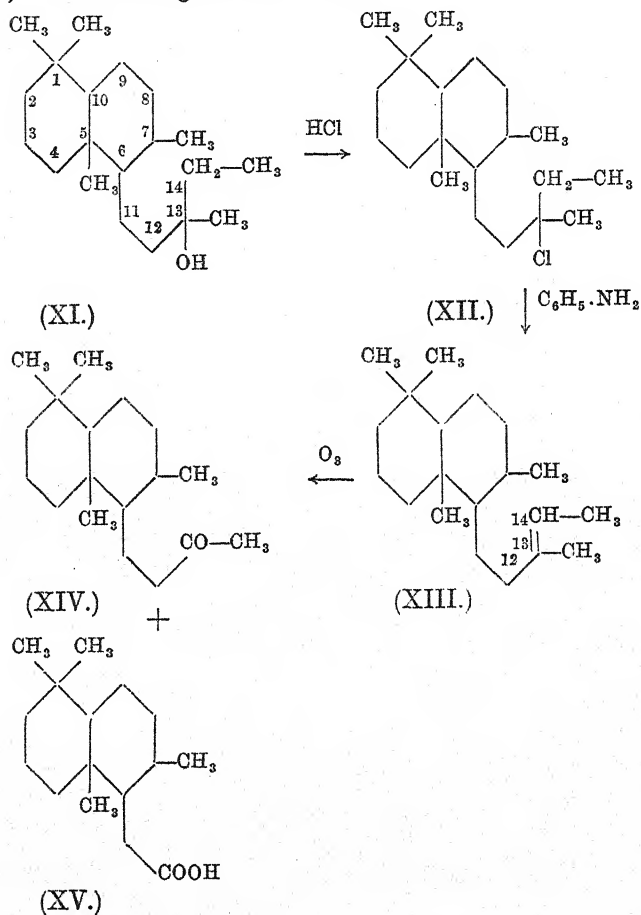
\* The quantitative estimation of methane liberated by the action of an hydroxy compound on methyl magnesium iodide:



(*Ber.*, 1907, 40, 2023.)

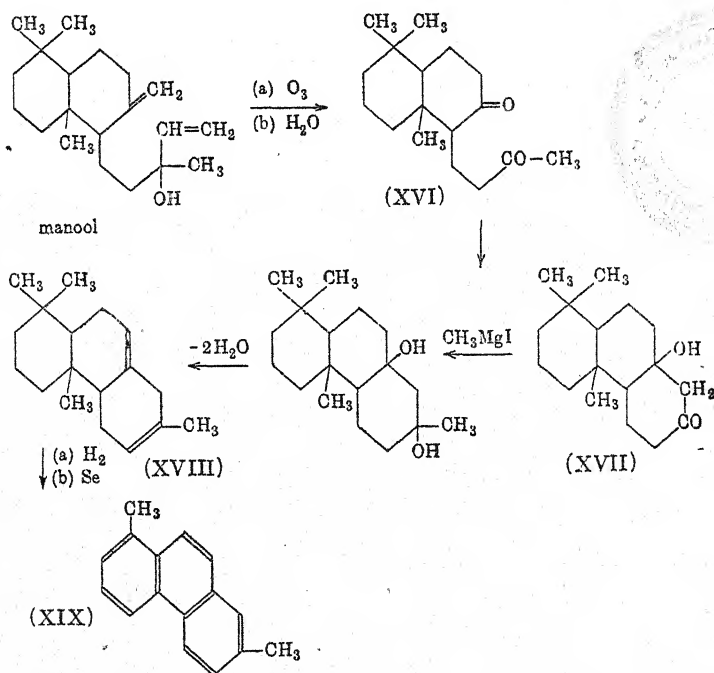
<sup>1</sup> Hosking and Brandt, *Ber.*, 1935, 68, [B], 1311.

into the hydrochloride (XII.), which by the action of hot aniline yielded the unsaturated compound tetrahydromanoene (XIII.). This substance when ozonized and then treated with water was converted into a ketone,  $C_{18}H_{32}O$  (XIV.) and an acid,  $C_{16}H_{28}O_2$  (XV.). These changes are as follows.



It is evident that the hydroxyl group of manool is attached to carbon atom 13 giving rise to a double bond between carbon atoms 13 and 14 in compound (XIII.). Ozone attacks this molecule at the point of unsaturation and gives rise to the ketone (XIV.). The acid may be a product of further oxidation or may arise from a hydrocarbon isomeric with (XIII.) and having a double bond between carbon atoms 12 and 13.

The action of ozone on manool itself is interesting and supports the other evidence that a methylene group is situated at carbon atom 7. The ozonide of manool decomposes under the influence of water to yield a diketone,  $C_{17}H_{28}O_2$  (XVI.). The action of sodium ethoxide followed by alcoholic sodium hydroxide on the diketone brings about an internal aldol condensation to a tricyclic keto-alcohol,  $C_{17}H_{28}O_2$  (XVII.). The keto-alcohol with an excess of methyl magnesium iodide reacts in the normal way and then splits off two molecules of water, with the formation of the unsaturated hydrocarbon,  $C_{13}H_{28}$  (XVIII.). This hydrocarbon, when hydrogenated and then acted upon by selenium, yields 1:7-dimethylphenanthrene (XIX.).<sup>1</sup> The structural changes are—

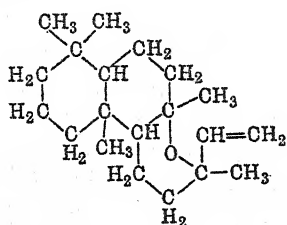


These last results are open to no other adequate interpretation, and taking into consideration the relationship between manool and manoyl oxide the structure of the alcohol may be regarded as settled.

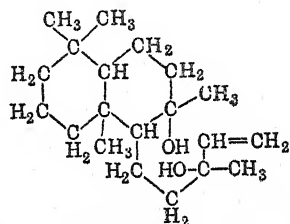
<sup>1</sup> Hosking, *Ber.*, 1936, 69, [B], 780.

## 4. Sclareol

This compound of molecular formula,  $C_{20}H_{36}O_2$  is a dihydric alcohol.<sup>1</sup> The splitting off of formaldehyde on ozonolysis, points to the presence of a terminal methylene group. Dehydrogenation of sclareol with selenium gives rise to 1:2:5-trimethylnaphthalene.<sup>2</sup> Sclareol is acted upon by hydrogen chloride producing manoene trihydrochloride, and if dihydro-sclareol is treated in the same way dihydromanoene dihydrochloride is formed. These properties of sclareol leave no doubt about its general molecular structure, and it is looked on as being the hydration product (XX.) of manoyl oxide, having one hydroxyl group attached at carbon atom 7 and another at position 13. The structure of manoyl oxide (XXI.) is given for comparison.



(XXI) manoyl oxide



(XX) sclareol

<sup>1</sup> Volmar and Jermstad, *Compt. rend.*, 1928, 186, 783; Janot, *ibid.*, 1930, 191, 847; 1931, 192, 845.

<sup>2</sup> Ruzicka and Janot, *Helv. Chim. Acta*, 1931, 645.



## CHAPTER VII

### THE TRITERPENE GROUP OF COMPOUNDS

#### A. INTRODUCTORY

THESE compounds containing thirty carbon atoms in the molecule have been isolated from numerous resins and saponins, and in the case of squalene from fish livers. As with many other substances of complex structure the purification of triterpene compounds was frequently very difficult, and the determination of molecular weights by the ordinary methods uncertain. Further uncertainties arose in the investigations, when it was discovered that groups, known to be present in the molecule, were inert towards some of the usual reagents. Thus ethylenic bonds failed to respond to catalytic reduction and carbonyl groups remained unaffected by sodium bisulphite solution or hydroxylamine.

With the exceptions of squalene and basseol the better known naturally occurring triterpene derivatives have a common pentacyclic structure. It has been established that the five-ring system has a reduced picene structure, from the fact that picones of known constitution have been identified amongst the products of dehydrogenation of practically all the members of this group.

#### B. THE SQUALENES

##### 1. *General*

The terpenes are so much associated with the vegetable kingdom that it is somewhat surprising to encounter a member of the class among the products of animal metabolism; all the more so, since hydrocarbons seem to offer but little hold for the reagents which play the main part in the vital processes of the vertebrates. And when it is further noted that squalene is a triterpene and thus more complex than most of the vegetable congeners, it must be admitted that it has exceptional points of interest.

Squalene was discovered by Tsujimoto,<sup>1</sup> who ascribed to it the composition  $C_{30}H_{50}$ ; and it appears to be identical with spinacene.<sup>2</sup> The hydrocarbon occurs in the livers of elasmobranch fish, chiefly in the *Squalidae* from which its name is derived. The determination of its constitution is not entirely completed; but the main lines have been worked out by Heilbron and his collaborators.

If six molecules of isoprene united to form an open chain, the resulting compound would obviously have the formula  $C_{30}H_{48}$ ; and the original twelve ethylenic linkages would be reduced to seven during the process of chain-formation. Saturation of one of these double bonds by hydrogen would yield a compound containing six ethylenic bonds and having the composition  $C_{30}H_{50}$ , which is the same as that of squalene. As a first guess, therefore, it is worth while to consider whether squalene has a constitution which in any way corresponds to this conception.

## 2. The Structure of Squalene

I. When squalene is reduced with hydrogen and a nickel catalyst, the hydrogenation proceeds through six well-marked stages; and the final product is squalane,  $C_{30}H_{62}$ . If the reduction is stopped after the hydrogen absorbed is just sufficient to saturate five double bonds, the product is not homogeneous; from which it appears that the original "squalene" may be a mixture of isomers.

II. When squalene is treated with hydrogen chloride, the product on analysis proves to have the composition  $C_{30}H_{56}Cl_6$ , whence it seems clear that squalene contains six ethylenic bonds. Examination shows that this product is a mixture of three separable, crystalline, hexahydrochlorides, which confirms the view that the original "squalene" is really a mixture of three isomeric hydrocarbons.\*

III. From each of these isomeric hexahydrochlorides, a hydrocarbon  $C_{30}H_{50}$  can be regenerated by the same method as is employed for this purpose among the ordinary terpenes.

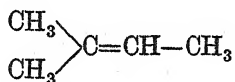
<sup>1</sup> Tsujimoto, *J. Chem. Ind. Japan*, 1906, 9, 953.

<sup>2</sup> Chapman, *J.*, 1917, 111, 56

\* An alternative possibility is that the original material is homogeneous, but undergoes isomerization in presence of hydrogen chloride or at the temperature  $150^{\circ}C$ . which is required for catalytic reduction.

IV. When boiled with acetic anhydride containing 1 per cent. of sulphuric acid, squalene passes through a series of isomeric changes; and from refractive index measurements it appears that the first product is a bicyclic compound; then a tricyclic isomer is produced; and in the final stage, only two double bonds seem to be left in the molecule. Here, again, the resemblance to the terpenes is striking. Further, this power of ring-closure is lost when squalene is partially reduced by taking up three, four or five molecules of hydrogen per molecule of the hydrocarbon.

V. Dry distillation of squalene yields products which, on analysis, were found to have compositions corresponding to  $C_5H_8$ ,  $C_{10}H_{16}$ , and  $C_{15}H_{24}$ . The lowest-boiling of these hydrocarbons was proved to be an amylene; and since on oxidation with permanganate it yielded acetone, its structure must be:—



The isolation of this substance, having the same skeleton as isoprene, tends further to confirm the idea that squalene belongs to the terpene class. Even more interesting is the fact that among the higher-boiling decomposition products of squalene there appears a hydrocarbon with physical constants which agree surprisingly with those of the sesquiterpene bisabolene.

VI. By treating squalene in acetone solution with solid permanganate, two ketones were obtained. One of these was identified as dihydro- $\psi$ -ionone; the other was, almost certainly,\* methyl-heptenone.

VII. Oxidation with chromyl chloride in carbon disulphide yielded formaldehyde, acetaldehyde, and succinic acid.

VIII. Ozonolysis of squalene in the usual way led to the detection of a number of fission products, of which the following are the most important: carbon dioxide (8.5 per cent.), formaldehyde, formic acid, succinic acid (28 per cent.), acetone, lævulinic acid, lævulinic aldehyde, and a complex ozonide,  $C_8H_{14}O_6$ , which appears to be derived from methyl-heptenone.

\* As will be seen later, though methyl-heptenone was not completely identified here, there is other evidence which leaves no doubt as to the nature of this ketonic fission-product.

IX. From the results just described, it is evident that oxidation splits up the squalene molecule too completely, leaving intact no fragments of a size sufficient to act as guides to the molecular structure. A way round this difficulty is found by reducing squalene with hydrogen sufficient to saturate five out of the six double bonds; and then ozonizing the reduced material. From what has already been said, it is clear that here the ozone is being applied to a mixture of isomeric hydrocarbons. By this method, the following substances were obtained among the disruption products: methyl-heptenone, hexahydro- $\psi$ -ionone a ketone with the formula  $C_{19}H_{33}O$ , another ketone containing twenty-three or twenty-four carbon atoms, as well as  $\gamma$ -methyl-*n*-valeric acid,  $C_6H_{13}.COOH$ , and 4:8-dimethyl-nonoic acid,  $C_{10}H_{21}.COOH$ . Finally, an acid was detected corresponding to the formula  $C_{16}H_{33}.COOH$ .<sup>1</sup>

The evidence contained in sections I.-IX. above is not sufficient to determine the structures of the squalenes in every detail; but there are facts enough to allow the broad outlines of the squalene constitutions to be laid down.

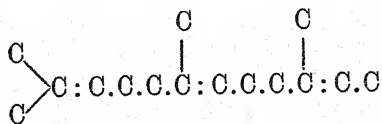
From I., it is plain that "squalene" is a mixture of isomers.

From II., it follows that "squalene" is a mixture of three isomers, each of which contains in its structure six double bonds.

From III., it is clear that the squalenes have a strong resemblance to the olefinic terpenes.

From IV., the closeness of this parallelism becomes even more apparent.

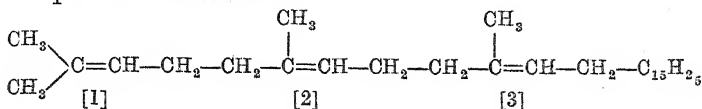
From V., it seems evident that at least one of the squalene isomers must contain the skeleton:—



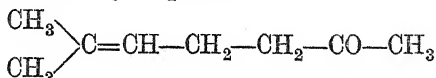
since this is the open chain corresponding to the grouping of atoms in bisabolene. Thus, at a single stroke, the arrangement of fifteen out of the thirty carbon atoms in this squalene chain has been ascertained; and by filling in the necessary hydrogen atoms

<sup>1</sup> Heilbron, Kamm, and Owens, *J.*, 1926, 1630; Heilbron, Hilditch, and Kamm, *ibid.*, 3131; Harvey, Heilbron, and Kamm, *ibid.*, 3136; Heilbron, Owens, and Simpson, *J.*, 1929, 873; Heilbron and Thompson, *ibid.*, 883.

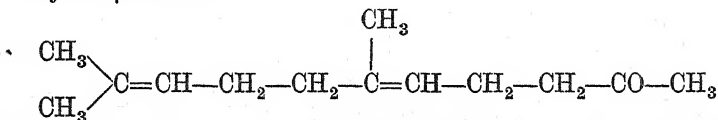
and tacking on the missing complex, the following formula for the squalene is obtained :—



This structure is in agreement with the facts mentioned in VI., as very little consideration will show. If the double bond marked [1] remains intact while oxidation breaks the bond marked [2], then methyl-heptenone :



will appear as a decomposition product. If both the double bonds [1] and [2] remain unaffected, whilst the chain is oxidized at the ethylenic linkage [3], the result will be the formation of dihydro- $\psi$ -ionone :

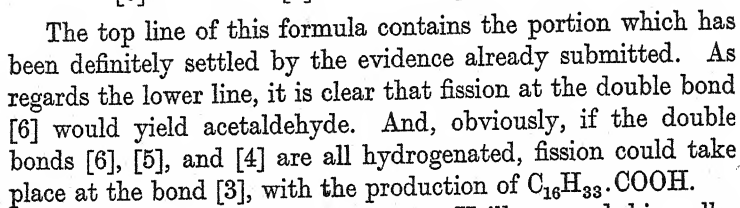


With the data summarized in VII., the formula is only in partial agreement. Succinic acid would result from oxidative rupture of the bonds [1] and [2] or of the bonds [2] and [3]. But the production of formaldehyde and acetaldehyde cannot so easily be accounted for, and this point must be reserved for later consideration in connection with the remainder of the structure which has been treated en bloc in the foregoing formulation.

The facts mentioned in VIII. can, in part, be brought into conformity with the formula. Oxidation at the bond [2] would yield methyl-heptenone ; and from this, in turn by further oxidation, the production of acetone, lævulinic aldehyde, lævulinic acid, and succinic acid could be produced.

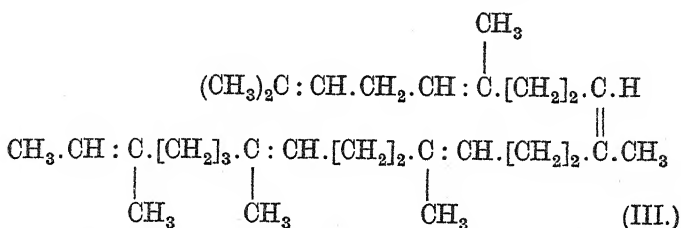
Turning now to the final series of facts grouped under IX., it is evident that two of the fragments are mutually complementary. Hexahydro- $\psi$ -ionone,  $\text{C}_{13}\text{H}_{26}\text{O}$ , and the acid  $\text{C}_{16}\text{H}_{33}\cdot\text{COOH}$  between them contain the complete set of thirty carbon atoms in squalene ; and it seems clear that these two compounds arise through a scission of the molecule at the double bond [3].

On the basis of the foregoing evidence, Heilbron and his


$$\text{(CH}_3\text{)}_2\text{C}:\text{CH}.\text{CH}_2.[\text{CH}_2.\underset{\text{CH}_2}{\underset{\parallel}{\text{C}}}.\text{CH}_2.\text{CH}_2]_4.\text{CH}_2.\underset{\text{CH}_3}{\underset{|}{\text{C}}}:\text{CH}.\text{CH}_3 \quad (\text{II.})$$

Neither of the foregoing formulae accounts satisfactorily for the production of  $\gamma$ -methylvaleric acid and 4:8-dimethylnonoic acid. The possibility that these are oxidation products of methylheptenone and hexahydro- $\psi$ -ionone must be excluded, as the conditions employed in the decomposition of the ozonides rule out such a solution completely. Further, along with the acid  $C_{10}H_{21}.COOH$  is found the ketone  $C_{19}H_{38}O$ ; and these two fragments are obviously complementary, since together they contain the whole thirty carbon atoms of the squalene chain. Obviously, to produce these fragments, the chain must break between the eleventh and twelfth carbon atoms from one end of it; and at this point there must be a double bond. No such bond is found in this position in either of the foregoing structures; so that a third formula is needed to account for these facts:—



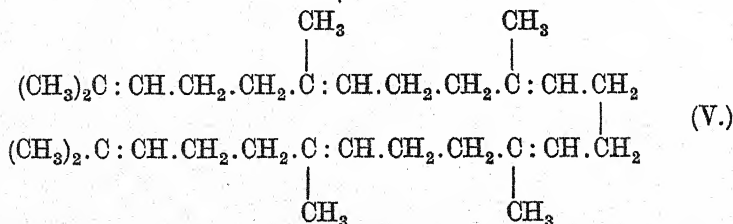
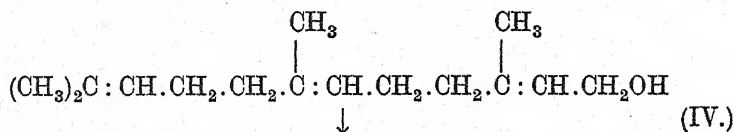


If this compound were reduced until the only double bond left intact was that which is printed vertically on the right-hand side of the formula above, then on oxidation this bond would break and the fragments of the squalene would be two in number: an acid,  $\text{C}_{10}\text{H}_{21} . \text{COOH}$  (4:8-dimethylnonoic acid), from the reduced top section; and the ketone  $\text{C}_{19}\text{H}_{38}\text{O}$  from the section indicated in the lower line of the formula.

Further, if the single unreduced bond in the decahydro-squalene lies between the sixth and seventh atoms in the top line of the formula, the ozonolysis should yield  $\gamma$ -methyl-*n*-valeric acid, which is again in agreement with the experimental results.

### 3. A Synthetic Squalene

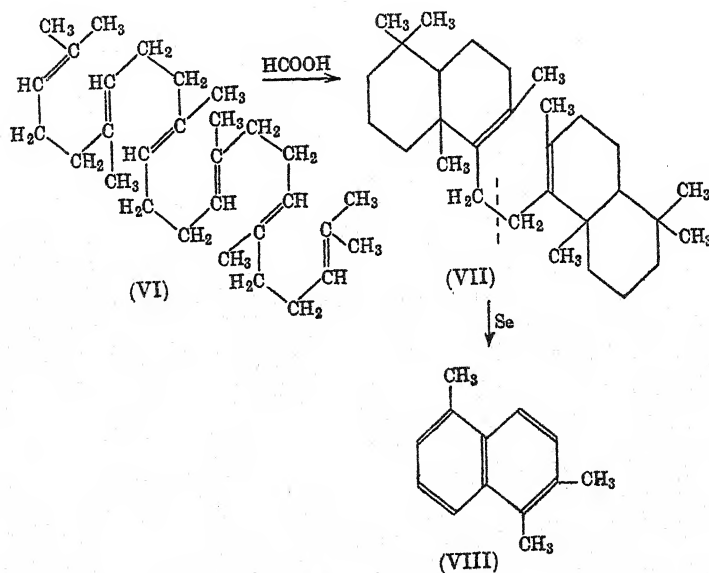
A squalene has been synthesized from farnesol in the following way.<sup>1</sup> Farnesol was converted into farnesyl bromide by the action of phosphorus tribromide. Under the influence of magnesium, bromine was eliminated from two molecules of the bromide with the formation of a squalene. Farnesol,  $\text{C}_{15}\text{H}_{26}\text{O}$  has the structure (IV.), and it follows that the squalene,  $\text{C}_{30}\text{H}_{50}$ , produced, must be given the formula (V.) shown below.



<sup>1</sup> Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, 14, 78.



Two hexachlorides of this isomer proved to be identical with chlorides prepared from natural squalene. When squalene is heated under reflux with formic acid isomerization occurs in stages through *dicyclo-* and *tricyclo-*isomers to *tetracyclosqualene* containing two double bonds. This tetracyclic compound is of interest as it yields, like several diterpene derivatives, and the triterpene lupeol, 1:2:5-trimethylnaphthalene on treatment with selenium.<sup>1</sup> The steps from squalene (VI.) through *tetracyclosqualene* (VII.) to 1:2:5-trimethylnaphthalene (VIII.) may be formulated as follows:—



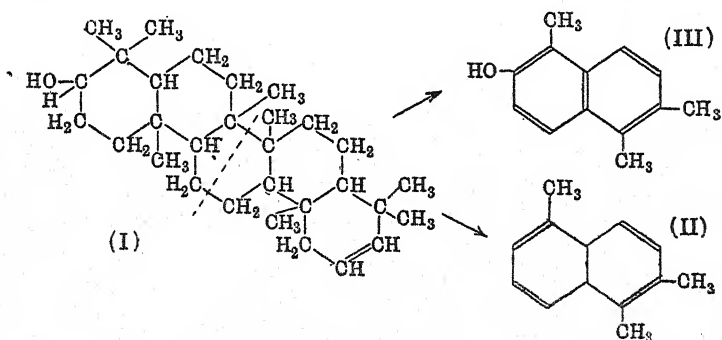
It is evident that the squalene (V.) obtained by synthesis is identical with one of the natural squalenes. Inspection of the structures suggested by Heilbron and his collaborators for the three isomers shows that, on the chemical evidence, structures (II.) and (III.) must be retained. It is preferable, however, to replace structure (I.) by structure (V.) for the remaining isomer.

<sup>1</sup> Heilbron, Kamm, and Owen, *loc. cit.*; Heilbron and Wilkinson, *J.*, 1930, 2546.

## C. LUPEOL (LUPENOL)

## 1. General

Lupeol has been isolated from plant species, such as *Sapotaceae*, *Rutaceae* and *Leguminosae*. It is an alcohol of molecular formula  $C_{30}H_{50}O$ . It is related to squalene in so far as it yields, like tetracyclosqualene, 1:2:5-trimethylnaphthalene (II.) on dehydrogenation with selenium. At the same time some 6-hydroxy-1:2:5-trimethylnaphthalene (III.) is produced.<sup>1</sup> Catalytic hydrogenation of lupeol is readily effected and shows that there is one ethylene linkage in the molecule. Taking into consideration its molecular formula and the degree of unsaturation lupeol must have a pentacyclic structure. From its relationship to symmetrical squalene lupeol was given the provisional structure (I.), the double bond being placed in an outer ring on account of the relative ease of addition of hydrogen.

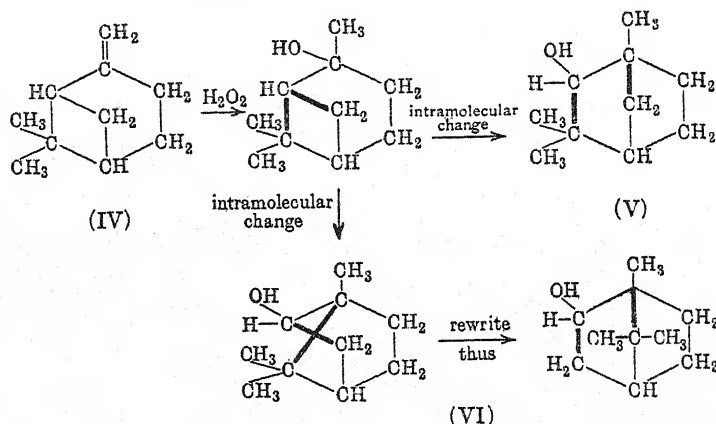


## 2. The Structure of Lupeol

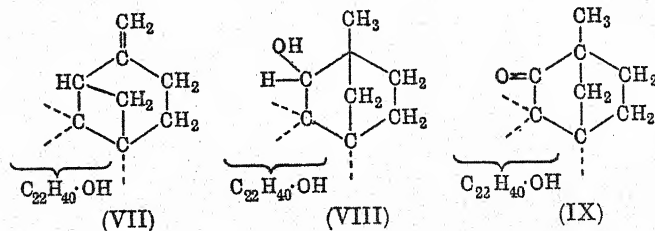
In the light of further investigations this structure, however, will have to be modified. When lupeol was converted into its acetate and then treated with ozone a considerable amount of formaldehyde was produced. This points to the presence of an exocyclic double bond in the molecule. Inspection of structure (I.) shows that the replacement of one of the methyl radicals by a methylene group is not feasible as each methyl group is attached to a tertiary carbon atom. Consequently in a revised formula one of the methyl groups may be replaced by a methylene

<sup>1</sup> Ruzicka and van Veen, *Z. physiol. Chem.*, 1929, 184, 69; Ruzicka, Furter, Pieth, and Schellenberg, *Helv. Chim. Acta*, 1937, 20, 1564.

group in a new position.<sup>1</sup> Lupenyl acetate may be oxidized by chromic anhydride to a keto-acetate,  $C_{32}H_{52}O_3$ , which contains the original acetate complement of carbon. On hydrolysis the keto-alcohol,  $C_{30}H_{50}O_2$  is obtained. On reduction with sodium and alcohol the keto-acetate yields a saturated dihydric alcohol,  $C_{30}H_{52}O_2$ . This same dihydric alcohol is formed when lupenyl acetate is treated with hydrogen peroxide and then hydrolysed. The net result of the action of hydrogen peroxide and hydrolysis is to effect the addition of the elements of one molecule of water to lupeol. This is reminiscent of the action of hydrogen peroxide on  $\beta$ -pinene (IV.), converting it into fenchyl alcohol (V.) and borneol (VI.) as follows <sup>2</sup> :—



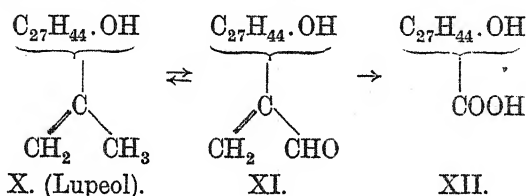
As the action of hydrogen peroxide on lupenyl acetate is similar, it is considered that a bridged ring and neighbouring double bond are also present in lupeol. The partial formula of lupeol is therefore (VII.), that of the dihydric alcohol, (VIII.), and that of the keto-alcohol, (IX.).



<sup>1</sup> Heilbron, Kennedy, and Spring, *J.*, 1938, 329; Duerden, Heilbron, McMeeking, and Spring, *J.*, 1939, 322.

<sup>2</sup> Henderson and Chisholm, *J.*, 1924, 125, 107.

On the other hand the opinion is held that the ethylenic linkage forms part of an *isopropenyl* group, as oxidation of lupeol (X.) with selenium dioxide yields an  $\alpha\beta$  unsaturated aldehyde (XI.), which reverts to lupeol on reduction. The aldehyde can be oxidized to an acid (XII.) containing two carbon atoms less than lupeol.<sup>1</sup> Other reactions of lupeol can be explained on the same basis.<sup>2</sup> The chemical changes mentioned may be represented as follows:—



The topic must be left at this interesting stage, as no good purpose would be served by attempting to write down a complete structure for the lupeol molecule.

## D. HEDERAGENIN AND OLEANOLIC ACID

### 1. General Relationships

Hederagenin has been isolated from soapnuts, *Sapindus*, and ivy leaves, and oleanolic acid from the leaves of the olive tree, *Olea Europaea*, Linné, sugar beet and cloves. Hederagenin is an unsaturated dihydroxymonobasic acid,  $\text{C}_{30}\text{H}_{48}\text{O}_4$  (I.), whilst oleanolic acid is a similar monohydroxy acid,  $\text{C}_{30}\text{H}_{48}\text{O}_3$  (II.).<sup>3</sup>

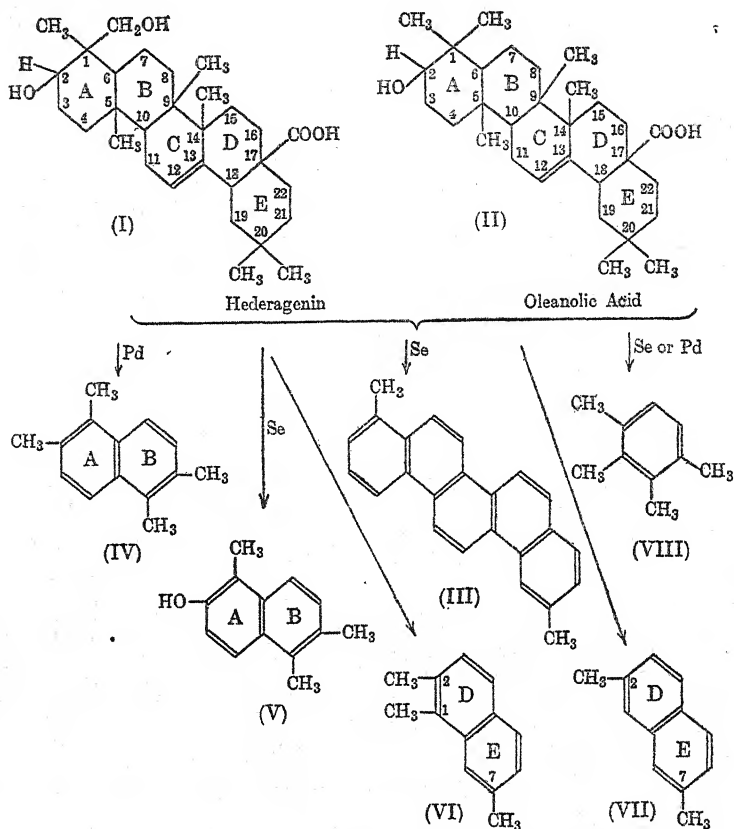
On dehydrogenation with selenium or palladium-carbon each yields 1:8-dimethylpicene (III.), 1:2:5:6-tetramethylnaphthalene (IV.), 6-hydroxy-1:2:5-trimethylnaphthalene (V.), 1:2:7-trimethylnaphthalene (VI.), 2:7-dimethylnaphthalene (VII.), and 1:2:3:4-tetramethylbenzene (VIII.).<sup>4</sup> Taking the molecular formulae, the isoprene rule and their reactions into consideration the following structures (I.) and (II.) were devised for hederagenin and oleanolic acid.

<sup>1</sup> Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, 23, 1311.

<sup>2</sup> Jones and Meakins, J., 1940, 456.

<sup>3</sup> Winterstein and Stein, *Z. physiol. Chem.*, 1931, 208, 9; 1931, 211, 5; Ruzicka and Furter, *Helv. Chim. Acta*, 1932, 15, 472.

<sup>4</sup> Ruzicka, Huyser, Pfeiffer, and Seidel, *Annalen*, 1929, 471, 25; Ruzicka et al., *Helv. Chim. Acta*, 1932, 15, 431; Ruzicka et al., *ibid.*, 1934, 17, 442

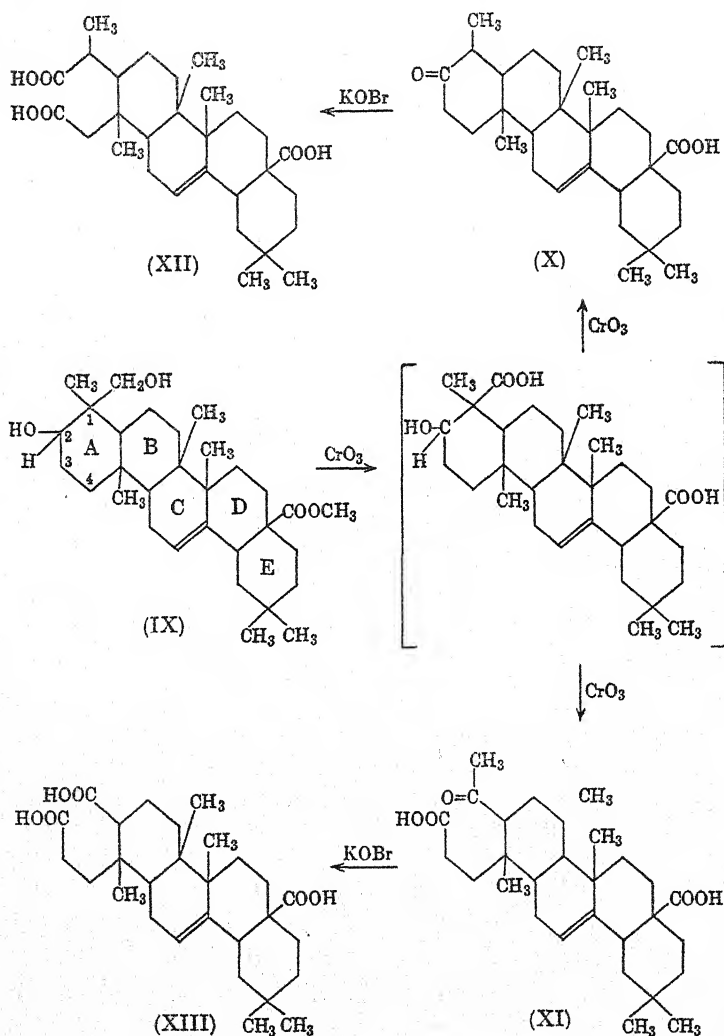


The breaking of the triterpene molecule through ring C accounts satisfactorily for the formation of the derivatives according to the above scheme. In the case of 1:2:5:6-tetramethylnaphthalene (IV.) it is considered that dehydration accompanied by migration of a methyl group from carbon atom 1 to carbon atom 2 takes place before dehydrogenation (see structures (I.) and (IV.)).<sup>1</sup> The broad outlines of the hederagenin and oleanolic acid molecules are, therefore, established, and the positions of two methyl groups (positions 1 and 20) and one hydroxyl group (position 2) fixed. The further problems are to place the carboxyl group, the remaining methyl groups, the ethylenic linkage, and, in the case of hederagenin, the second hydroxyl group.

<sup>1</sup> Ruzicka, Schellenberg, and Goldberg, *Helv. Chim. Acta*, 1937, 20, 791.



second hydroxyl group is attached to carbon atom I. The evidence is as follows: when the methyl ester of hederagenin (IX.) is oxidized with chromic acid a carbon atom is split off and a mixture of a keto-acid,  $C_{29}H_{44}O_3$  (X.), and a keto-dicarboxylic acid,  $C_{29}H_{44}O_5$  (XI.) is obtained.<sup>1</sup> When the keto-

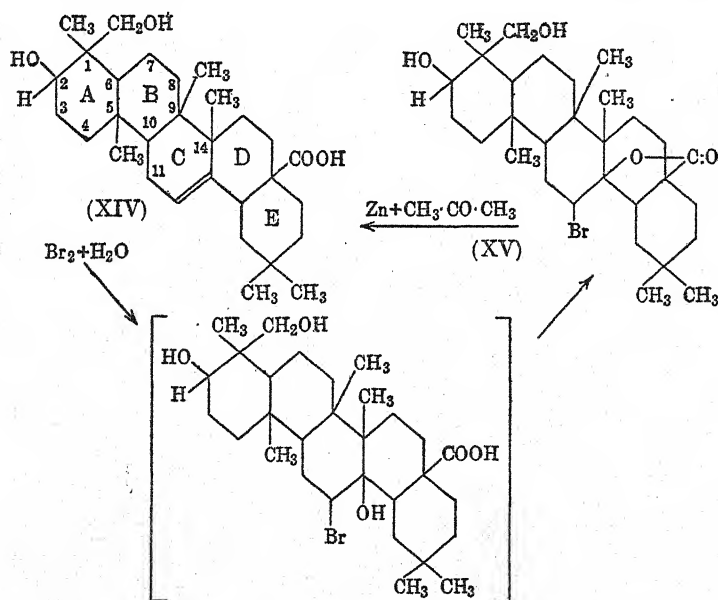


<sup>1</sup> Jacobs and Gustus, *J. Biol. Chem.*, 1926, 69, 641.



acid (X.) is oxidized with hypobromite a tribasic acid,  $C_{29}H_{44}O_6$  (XII.) results. Under similar treatment the keto-dicarboxylic acid loses a carbon atom with the formation of a tribasic acid,  $C_{28}H_{42}O_6$  (XIII.). These results can best be interpreted by placing the two hydroxyl groups of hederagenin in positions 1:3 relative to each other. The changes are formulated as shown on p. 214.

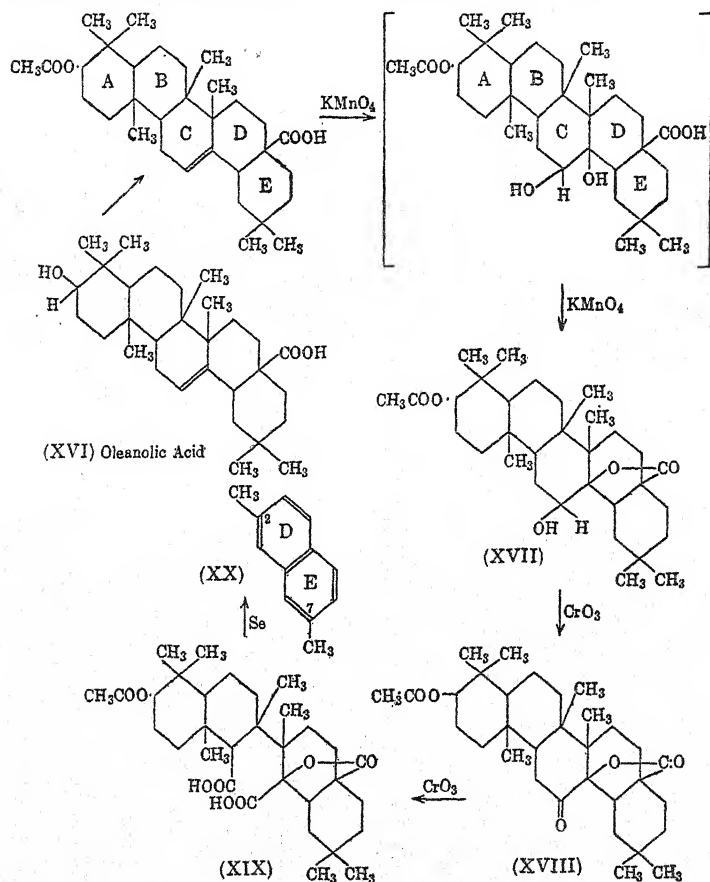
Taking into consideration the structures of other terpene derivatives such as agathic dicarboxylic acid and abietic acid and the migration of a methyl group in the formation of 1:2:5:6-tetramethylnaphthalene (IV.) by dehydrogenation, the primary alcohol group of hederagenin is allocated to carbon atom 1 of the molecule. It follows that ring A of oleanolic acid (II.) has the structure assigned to it. It has been indicated that the product of dehydrogenation 2:7-dimethylnaphthalene (VII.) is thought to arise from rings D and E of the oleanolic acid or hederagenin molecule, pointing to ring C as the weak part of the molecule and possibly the seat of the double carbon bond. The



<sup>1</sup> Kitasato, *Acta Phytotchim.*, 1936, 9, (1), 43; Kitasato and Sone, *ibid.*, 1932, 6, (2), 305; Kitasato, *ibid.*, 1933, 7, (1), 1.

position of the double bond is important, as hederagenin and oleanolic acid are considered to be  $\gamma$   $\delta$ -unsaturated acids. When hederagenin (XIV.) is brominated it loses its acid character. A neutral compound such as lactone formed from an hydroxyl group and the carboxyl group is not produced, as the action of methyl magnesium iodide shows that the two hydroxyls of the original hederagenin are still in the new neutral molecule (XV.). Hederagenin can be regenerated from this neutral compound by the action of zinc dust in acetone.

These changes are formulated as shown on p. 215, assigning a bromo- $\gamma$ -lactone structure to the neutral compound (XV.).<sup>1</sup>



<sup>1</sup> Kirasato, *Acta Phytochem.*, 1936, 9, 61; 1937, 10, 199.

. When oleanolic acid (XVI.) is converted into its acetyl derivative, to stabilize the terminal ring carrying the hydroxyl group, and then oxidized with potassium permanganate, one of the products is an hydroxy-lactone,  $C_{32}H_{50}O_5$  (XVII.).<sup>1</sup> Oxidation of this compound by chromic acid yields a keto-lactone,  $C_{32}H_{48}O_5$  (XVIII.). Further oxidation with chromic acid gives rise to a lactone-dicarboxylic acid,  $C_{32}H_{48}O_8$  (XIX.), which on dehydrogenation breaks down to give 2:7-dimethylnaphthalene (XX.).<sup>2</sup> One way in which these changes may be illustrated is as shown on p. 216.

As already mentioned the product of dehydrogenation, 2:7-dimethylnaphthalene, is thought to arise from rings D and E of oleanolic acid. Its formation from the lactone dicarboxylic acid also points to ring C, as the position of the double bond in oleanolic acid. In these illustrations the carboxyl group has been placed at carbon atom 17, and the four methyl groups at the angle carbon atoms 5, 9, 14, and 20. No direct evidence is available with regard to the exact positions of these methyl groups. They are, however, eliminated with one other in the conversion of oleanolic acid into 1:8-dimethylpicene. Such eliminations are characteristic of compounds containing angle or *gem* groups.

Many other products of oxidation of oleanolic acid and hederagenin have been prepared, and the bearing of their nature on the problem of the fine structure of the triterpenes studied. It may be noted that a structure for oleanolic acid with the carboxyl group attached at carbon atom 20 and a methyl group at carbon atom 17 gives a reasonable representation of its reactions.<sup>3</sup>

## E. THE AMYRINS (AMYRENOLS)

### 1. General

The amyryns may be isolated from the oleoresin Manila Elemi, and have been found in numerous other resins and saps. Two compounds,  $\alpha$ - and  $\beta$ -amyrin, have been identified. There

<sup>1</sup> Aumüller, Schicke, and Wedekind, *Annalen*, 1935, 517, 211.

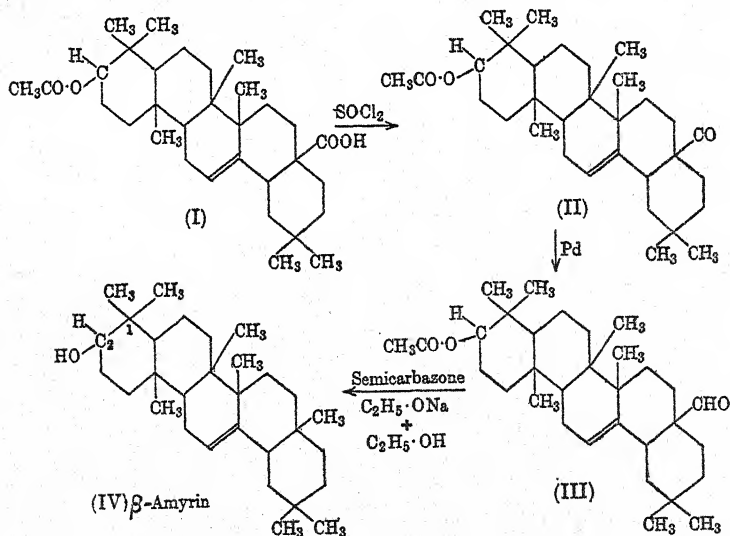
<sup>2</sup> Ruzicka and Hofmann, *Helv. Chim. Acta*, 1936, 19, 114; Kitasato, *Acta Phytochem.*, 1936, 9, (1), 75.

<sup>3</sup> Bilham and Kon, *J.*, 1941, 552.

is complete similarity in the behaviour of these two substances and they are probably stereo-isomeric.<sup>1</sup> The molecular formula is  $C_{30}H_{50}O$ .

## 2. Decomposition Products and Structures

The oxygen atom is present in the molecule as part of a secondary alcohol group, as oxidation leads to the ketone amyrenone. The products of dehydrogenation with selenium are similar to those obtained from hederagenin and oleanolic acid, with the addition of 2-hydroxy-1:8-dimethylpicene.\* The position of the hydroxyl group in the pentacyclic system is consequently fixed at position 2 (IV.). This is confirmed by the conversion of oleanolic acid into  $\beta$ -amyrin.<sup>2</sup> Acetyloleanolic acid (I.) was converted into the acid chloride,  $C_{32}H_{49}O_3Cl$  (II.) by means of thionyl chloride. The acid chloride was then catalytically reduced, using palladium on barium sulphate, to the corresponding aldehyde,  $C_{32}H_{50}O_3$  (III.). The aldehyde semicarbazone was treated with sodium ethoxide in alcohol and  $\beta$ -amyrin (IV.) isolated. Taking the structure of acetyl oleanolic acid to be (I.) the following scheme represents the changes:—



<sup>1</sup> Vesterberg, *Ber.*, 1887, 20, 1242; 1890, 23, 3186.

\* See page 212.

<sup>2</sup> Ruzicka and Scheilenberg, *Helv. Chim. Acta*, 1937, 20, 1553.

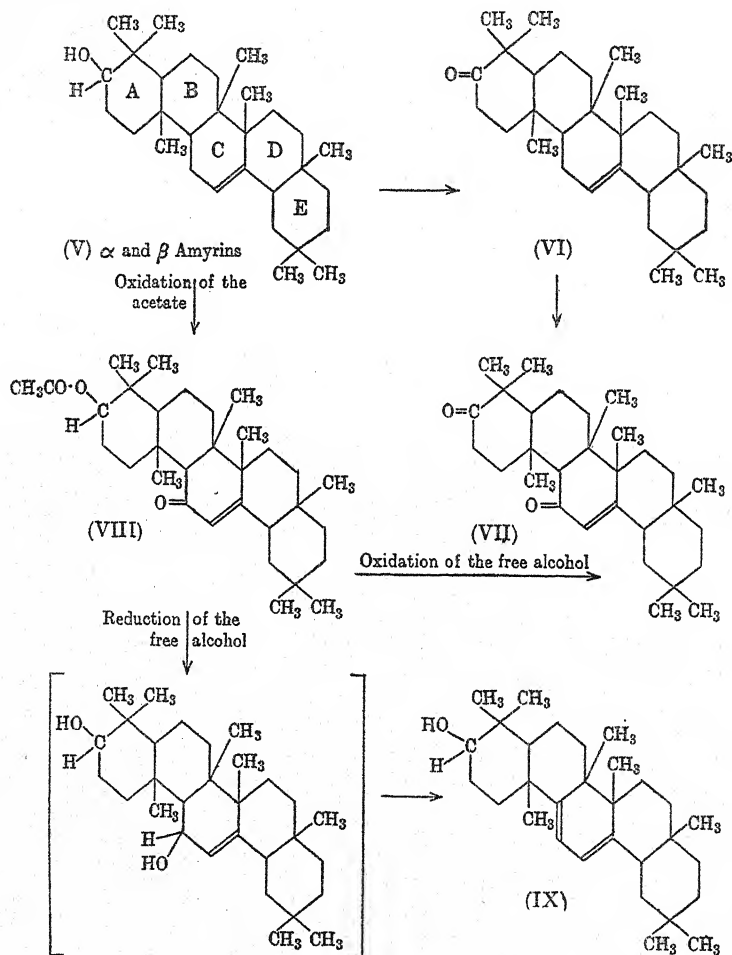
The double carbon bond of the amyryns is inert to catalytic reduction by means of hydrogen and platinum black. The existence of the double bond has, however, been demonstrated indirectly in the following way.<sup>1</sup> When  $\alpha$ -amyrin (V.) was oxidized with chromic acid it yielded the monoketone,  $\alpha$ -amyrenone (VI.), by transformation of the secondary alcohol group. Further oxidation produced a diketone,  $\alpha$ -amyrenedione,  $C_{30}H_{46}O_2$  (VII.). If the alcoholic hydroxyl group of  $\alpha$ -amyrin ( $\alpha$ -amyrenol) is protected by conversion into the acetate, and then oxidized,  $\alpha$ -amyrenonol (VIII.) is obtained, which can be further oxidized to  $\alpha$ -amyrenedione (VII.). The carbonyl group of  $\alpha$ -amyrenonol is inactive towards the usual ketonic reagents, but it shows the typical ultra-violet absorption spectrum of an  $\alpha\beta$ -unsaturated ketone. The presence of the ketonic group in  $\alpha$ -amyrenonol is further confirmed by its reduction by means of sodium in amyl alcohol to a dihydric secondary alcohol, which splits off water yielding dehydro- $\alpha$ -amyrin (IX.). When the acetate of this dehydro-derivative is treated with perbenzoic acid, it gives a monoxide. The parent substance,  $\alpha$ -amyrin itself, in the form of its acetate is completely inert to perbenzoic acid. It follows, therefore, that the dehydro-compound contains a new additional double carbon bond which is reactive. The absorption spectrum curve of the dehydro-acetate indicates that the bonds are conjugated. The identification of  $\alpha$ -amyrenonol as  $\alpha\beta$ -unsaturated ketone also confirms the unsaturated nature of  $\alpha$ -amyrin. The production of the carbonyl group in the  $\alpha\beta$  position to the double carbon bond in the conversion of  $\alpha$ -amyrin acetate into  $\alpha$ -amyrenonol acetate necessitates the presence of a  $-\text{CH}_2-$  group in the same position in  $\alpha$ -amyrin, and the formation of dehydro- $\alpha$ -amyrin leads to the conclusion that a  $-\text{CH}-$  grouping is adjacent to the  $-\text{CH}_2-$ . The scheme of structure, shown on p. 220, will make these different points clearer.

It may be concluded that  $\alpha$ -amyrin contains the grouping

$\text{>C}=\text{C}-\text{CH}_2-\text{CH}-$ , and this must be situated in a single cyclic system. The grouping has been placed in ring C with the

<sup>1</sup> Spring and Vickerstaff, *J.*, 1934, 1859; *ibid.*, 1937, 249; Beynon, Sharples and Spring, *ibid.*, 1938, 1233.

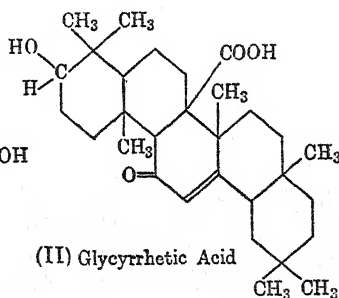
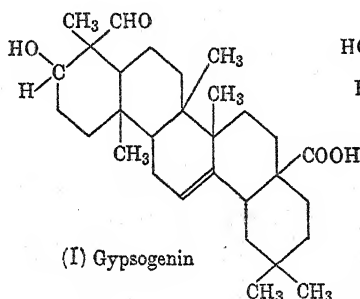
double bond between carbon atoms 12 and 13 (V.). In a similar way this grouping has been shown to be present in  $\beta$ -amyrin. Until more definite evidence is obtained with regard to the positions of all the methyl groups the structure (V.) may be adopted.



F. GYPSOGENIN, GLYCYRRHETIC ACID, ERYTHRODIOL,  
BETULIN AND BASSEOL

1. *Gypsogenin*

Gypsogenin,  $C_{30}H_{46}O_4$ , is closely related to both hederagenin and oleanolic acid.<sup>1</sup> It yields similar naphthalene and picene derivatives on dehydrogenation.<sup>2</sup> In addition to the secondary alcohol and carboxyl groups it contains an aldehyde group. When it is oxidized with chromic acid it yields a ketonic acid identical with that obtained by the similar oxidation of hederagenin. Gypsogenin may accordingly be given the provisional structure (I.) shown below, bringing it into line with hederagenin, oleanolic acid and the amyrsins.



2. *Glycyrrhetic Acid*

Glycyrrhetic acid has the molecular formula,  $C_{30}H_{46}O_4$ . Amongst the products of dehydrogenation with selenium, 2:7-dimethylnaphthalene, 1:2:7-trimethylnaphthalene and 1:8-dimethylpicene have been identified.<sup>3</sup> Three of the four oxygen atoms of the acid are accounted for by a carboxyl and a secondary alcoholic group. The fourth atom is in a ketonic group, as reduction of methylglycyrrhetate in the presence of platinic oxide gives rise to methyl deoxyglycyrrhetate. In this reduction the alcoholic hydroxyl is unaffected as the new product can be converted by the action of acetic anhydride into methyl acetyl-deoxyglycyrrhetate. The point of attack in the reduction is the

<sup>1</sup> Ruzicka and Giacomello, *Helv. Chim. Acta*, 1936, 19, 1136; 1937, 20, 299.

<sup>2</sup> Ruzicka et al., *Annalen*, 1929, 471, 25; *Helv. Chim. Acta*, 1932, 15, 1496.

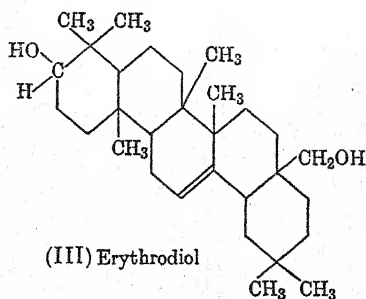
<sup>3</sup> Ruzicka et al., *Helv. Chim. Acta*, 1937, 20, 312; *Annalen*, 1929, 471, 25.



carbonyl group which is converted into a methylene group. This evidence of the ketonic nature of glycyrrhetic acid is supported by its absorption spectrum, which is typical of an  $\alpha\beta$  unsaturated ketone.<sup>1</sup> The conversion of glycyrrhetic acid by reduction of its carbonyl and carboxyl groups into  $\beta$ -amyrin gives conclusive evidence that in its principal features the structure of the acid is similar to those of the other hydropicene derivatives already considered in this section. In the change from glycyrrhetic acid to  $\beta$ -amyrin the acid was converted into acetyldeoxyglycyrrhetic acid by the method mentioned above. The carboxyl group was then reduced to a methyl group by the methods used successfully in the conversion of oleanolic acid into  $\beta$ -amyrin.\*<sup>2</sup> Consequently glycyrrhetic acid may be given the provisional structure (II.) shown above.

### 3. Erythrodiol

Erythrodiol contains both a primary and a secondary alcoholic group. The point of unsaturation in the molecule is chemically inert. When the primary alcohol group is oxidized to carboxyl, oleanolic acid results.<sup>3</sup> The formula (III.) comparable with the provisional structure adopted for oleanolic acid may therefore be written down for erythrodiol.



<sup>1</sup> Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, 20, 804; Ruzicka, Leuenberger, and Schellenberg, *ibid.*, 1937, 20, 1271.

\* See p. 218.

<sup>2</sup> Ruzicka and Marxer, *Helv. Chim. Acta*, 1939, 22, 195.

<sup>3</sup> Zimmermann, *Rec. Trav. chim.*, 1937, 57, 1200; *Helv. Chim. Acta*, 1936, 19, 247.

4. *Betulin*

Betulin has the molecular formula,  $C_{30}H_{50}O_2$ , and contains two alcoholic groups, one primary and the other secondary.<sup>1</sup> Unlike some of the other compounds of this group, betulin readily forms a dihydro-compound by reduction of the double carbon bond. When betulin monoacetate is oxidized with chromic acid followed by treatment with pyridine and acetic anhydride, acetylbetulin aldehyde is formed. The aldehyde semicarbazone on reduction yields lupeol.<sup>2</sup> Dehydrogenation of betulin gives rise to a picene derivative, 1 : 2 : 5 : 6-tetramethylnaphthalene, 6-hydroxy-1 : 2 : 5-trimethylnaphthalene, 1 : 2 : 7-trimethylnaphthalene and 1 : 2 : 3 : 4-tetramethylbenzene. No 2 : 7-dimethylnaphthalene has been isolated from the products of dehydrogenation by either selenium or palladium.<sup>3</sup> In ascribing a constitution to betulin, the relationship to lupeol, the absence of 2 : 7-dimethylnaphthalene in the products of dehydrogenation, and the nature of the double carbon bond will have to be considered carefully.

5. *Basseol*

Basseol has been obtained from shea-nut oil along with  $\beta$ -amyrin and lupeol.<sup>4</sup> Its molecular formula is  $C_{30}H_{50}O$ . It is a secondary alcohol and contains two double carbon bonds. The action of perbenzoic acid shows that the molecule absorbs two atomic proportions of oxygen. On the other hand catalytic reduction of basseol acetate gives rise to a dihydro-compound (VI.) only. Basseol appears, then, to contain one inert double bond. Spectroscopic examination of basseol acetate indicates that the double bonds are not conjugated. Basseol acetate can be readily isomerized by the action of bromine to  $\beta$ -amyrin acetate (VIII.).<sup>5</sup> Dehydrogenation of basseol produces 1 : 2 : 6-trimethylphenanthrene (VII.). The properties of basseol and its derivatives mentioned above can be satisfactorily explained by giving it the following structure (IV.) :—

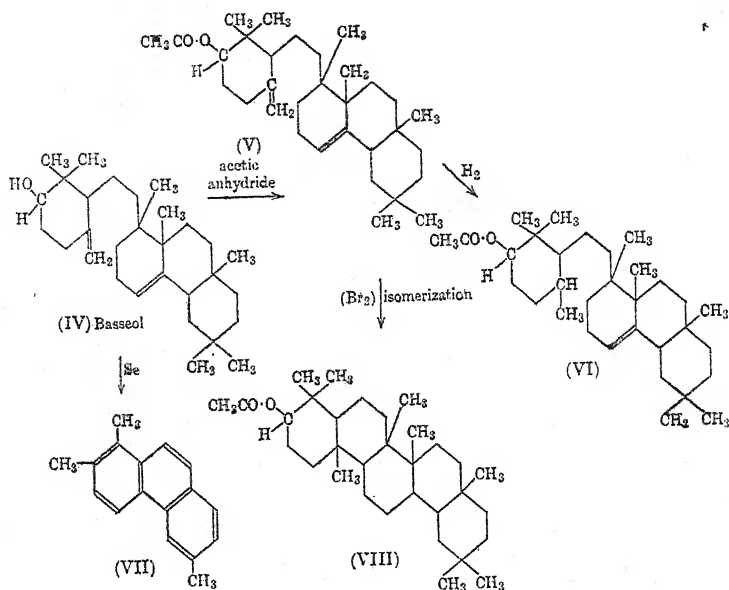
<sup>1</sup> Ruzicka, Brungger, and Gustus, *Helv. Chim. Acta*, 1932, 15, 634.

<sup>2</sup> Ruzicka and Brenner, *Helv. Chim. Acta*, 1939, 22, 1523.

<sup>3</sup> Ruzicka et al., *Annalen*, 1929, 471, 25 ; *Helv. Chim. Acta*, 1932, 15, 431.

<sup>4</sup> Heilbron, Moffet, and Spring, *J.*, 1934, 1583.

<sup>5</sup> Beynon, Heilbron, and Spring, *J.*, 1937, 989.



In concluding this brief account of the chemistry of the triterpenes, it must be emphasized that in the formulae shown, the positions allotted to some of the groups are provisional, and that further work on these compounds may lead to adjustments in the structures.



## CHAPTER VIII

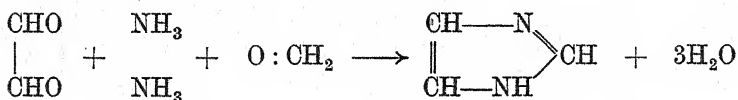
### VARIOUS GROUPS OF ALKALOIDS

In this chapter no attempt can be made to describe all the investigations which have been carried out upon these alkaloids during the last few years. Much of the work which has been done is of value mainly because it is paving the way towards a final solution of sundry constitutions; but in itself it is of little interest, since it is only a link in a chain of which we cannot as yet see the end. Consequently the inclusion of accounts of it here would serve very little purpose.

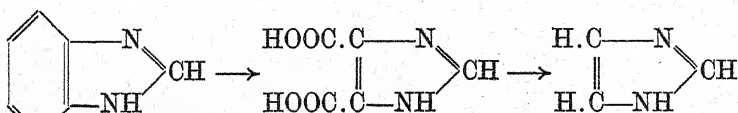
A number of fields have been completely cleared up in recent times, however, and it seems best to devote most of the space available here to some description of the results attained in these particular regions of the subject. A certain scrappiness of treatment is unavoidable, since the various alkaloidal groups which thus come under consideration are isolated from each other in almost every respect. Nevertheless, even this disjointedness will serve to depict fairly well the present condition of the research which is going on among the alkaloids.

#### A.—THE GLYOXALINE GROUP

The parent substance of the glyoxaline group may be obtained by condensing together glyoxal, ammonia, and form-aldehyde:



It may also be produced by oxidizing benzimidazole with permanganate and then heating the dicarboxylic acid so formed:



An examination of the purine structure will show that it may be regarded as containing a glyoxaline ring condensed with a pyrimidine nucleus; so that the purine derivatives may be considered as partly derived from glyoxaline: but it is not necessary to lay too much stress upon this relationship since the uric acid group is sufficiently distinct to permit of its being regarded as a class by itself.

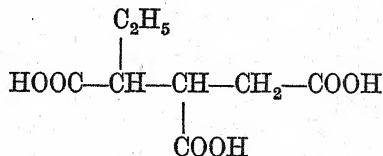
### 1. *The Constitutions of Pilocarpine, Isopilocarpine, and Pilocarpidine*

Pilocarpine occurs in jaborandi leaves in conjunction with several related alkaloids: pilocarpidine,<sup>1</sup> isopilocarpine,<sup>2</sup> pilosine,<sup>3</sup>  $\psi$ -pilocarpine,<sup>4</sup> and  $\psi$ -jaborine.\* The general structure of pilocarpine has been established in the following manner.

The composition of pilocarpine is  $C_{11}H_{16}N_2O_2$ . Although it contains two nitrogen atoms it does not yield an amide with acetyl chloride; so it is clear that both nitrogen atoms must be tertiary ones. Oxidation<sup>5</sup> with permanganate produces from pilocarpine a mixture of methyl urea, homopilocipic acid, and pilopic acid. As pilopic acid is derived from homopilocipic acid by further oxidation, it will be best to examine first the constitution of homopilocipic acid.

Homopilocipic acid is a lactonic acid, containing one lactone ring and one free carboxyl radicle. From the stability of the lactonic structure, the substance is evidently a  $\gamma$ -lactone. Its composition is  $C_8H_{12}O_4$ .

When fused with caustic potash, homopilocipic acid gives  $\alpha$ -ethyltricarballic acid:



<sup>1</sup> Harnack, *Annalen*, 1887, 238, 230.

<sup>2</sup> Petit and Polonowsky, *J. Pharm. Chim.* (vi.), 1897, 5, 370, 430; 6, 8.

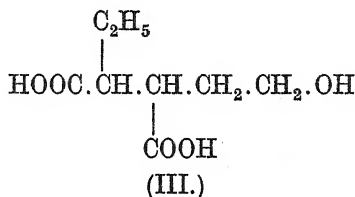
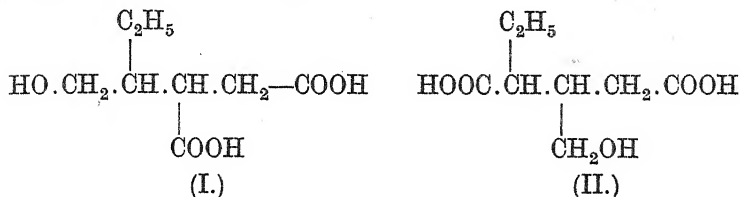
<sup>3</sup> Pyman, *P.*, 1912, 28, 267.

<sup>4</sup> Petit and Polonowsky, *Chem. Zentr.*, 1897 (i.), 1126.

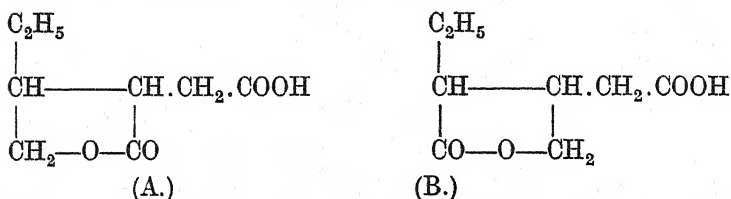
\* The supposed alkaloid jaborine appears to be a mixture (Jowett, *J.*, 1900, 77, 474, 851; 1901, 79, 581, 1331).

<sup>5</sup> Jowett, *J.*, 1900, 77, 474, 851; 1901, 79, 581, 1331; compare Pinner, *Ber.*, 1900, 33, 1424, 2537; 1901, 34, 727; 1902, 35, 204, 2443; 1905, 48, 1510.

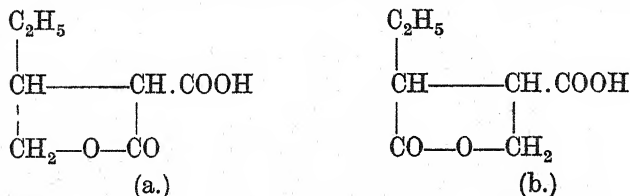
This substance must arise from a hydroxy-acid (the parent of the lactonic homopilopic acid) by the action of the potash ; and for this hydroxy-acid three formulæ are possible, from which we must select the correct one :



Now pilopic acid appears to be derived from homopilopic acid by loss of carbon dioxide and oxidation of the carbon atom which carried the destroyed carboxyl radicle. Of all the possible  $\gamma$ -lactonic formulæ derived from the three acids shown above, only two can fulfil this condition—



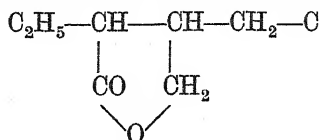
The corresponding formulæ for pilopic acid would therefore be :



Now, owing to the fact that in (a) there are two carboxyl radicles (one in lactone form) attached to the same carbon atom, we should expect such a compound to lose carbon dioxide easily

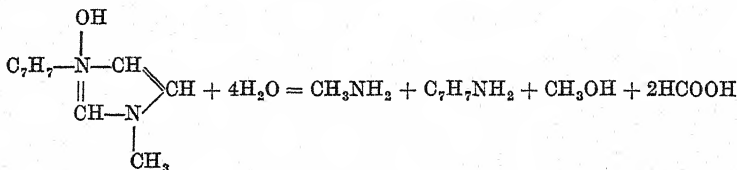
on heating as malonic acid does. Pilopic acid, however, is stable even at 200° C. It seems most probable, therefore, that pilopic acid has the formula (b); which leads us to the formula (B) for homopilopic acid.

By this reasoning, pilocarpine itself must contain the skeleton

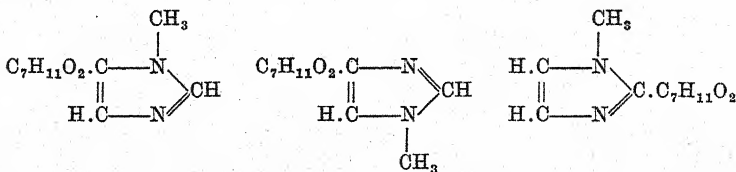


in addition to a group  $\text{C}_3\text{H}_5\text{N}_2$ , which disappears completely on oxidation. With regard to the structure of this last complex we must look for further evidence.

When derivatives of glyoxaline are allowed to interact with alkyl halides, ammonium compounds are formed which break down under the action of caustic potash, yielding primary amines. Now when pilocarpine is submitted to this series of reactions, it gives rise to equimolecular quantities of methylamine, methyl alcohol, and  $\text{C}_7\text{H}_7\cdot\text{NH}_2$ , plus two molecular proportions of formic acid. This decomposition can be accounted for by assuming that its methyl iodide addition product is transformed by caustic potash into an ammonium hydroxide of the following structure :—



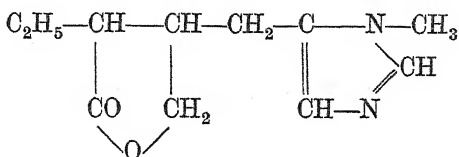
Thus pilocarpine itself may have one of the following structures :— \*



\* It is assumed that the union between the glyoxaline group and the rest of the molecule is originally through carbon, a wandering of the homopilopic group taking place during the decomposition.

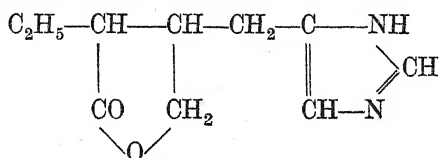


An examination of the dimethyl-glyoxalines by Pyman<sup>1</sup> led to the conclusion that pilocarpine must be a 1:5-derivative of glyoxaline. The following formula has therefore been ascribed to it:—



Pilocarpine.

The alkaloid pilocarpidine<sup>2</sup> appears to be the imine corresponding to pilocarpine, so that its structure can be expressed by



Pilocarpidine.

It will be observed that the pilopyl group of these compounds contains two asymmetric carbon atoms.

The oxidation of pilocarpine and *isopilocarpine* gives rise to the same products; which shows that the two substances are closely allied in structure. Their chemical properties are also very similar; and the absorption spectra of their nitrates are identical.<sup>3</sup> Further, pilocarpine and *isopilocarpine*, when treated with alcoholic potash, are both converted into an equilibrium mixture containing chiefly *isopilocarpine*. From evidence of this kind, Jowett<sup>4</sup> regards *isopilocarpine* as a stereoisomer of pilocarpine; and this view appears to cover all the more important reactions of the alkaloids.

These structures of the alkaloids and their decomposition products have been confirmed by syntheses. Pilopic<sup>5</sup> and homopilopic<sup>6</sup> acids have been prepared in the following way. Ethyl ethylsuccinate (IV.) and ethyl formate were condensed

<sup>1</sup> Pyman, *J.*, 1910, 97, 1814; 1922, 121, 2616.

<sup>2</sup> Späth and Kunz, *Ber.*, 1925, 58, [B], 513.

<sup>3</sup> Dobbie, *cf.* Hartley, *P.*, 1903, 19, 122.

<sup>4</sup> Jowett, *J.*, 1903, 83, 438; 1905, 87, 794.

<sup>5</sup> Tschitschibabin and Preobrashenski, *Ber.*, 1930, 63, [B], 460.

<sup>6</sup> Preobrashenski, Poljakova and Preobrashenski, *Ber.*, 1935, 68, [B], 850.

in the presence of alcoholic sodium ethoxide to yield formylethylsuccinate (V.), which on reduction by aluminium in moist ether was converted into a mixture of isomeric ethyl ethylitamalates (VI.). The action of heat split off alcohol from these isomers and yielded a mixture of stereoisomeric ethyl pilopates (VII.). From this mixture of esters the four compounds, *d*- and *l*-isopilopic and *d*- and *l*-pilopic acids (VIII.) were isolated. The next step, the conversion of pilopic acid into homopilopic acid, was accomplished through the acid chloride of *d*-pilopic acid (IX.). This compound was acted upon by diazomethane in ether with the formation of diazomethyl *d*-pilopoyl ketone (X.).<sup>1</sup> The ketone was then treated with an aqueous mixture of sodium hyposulphite and silver oxide and yielded *d*-homopilopic acid (XI.), identical with the acid from natural sources.

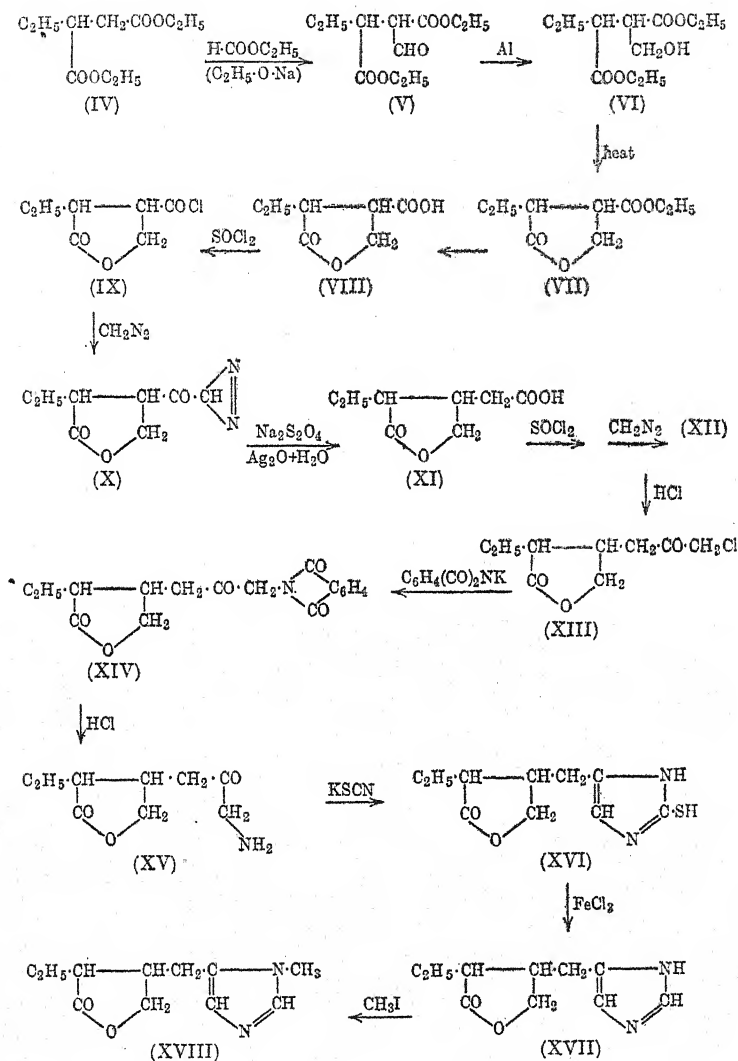
The final steps—production of *d*-pilocarpidine and *d*-pilocarpine<sup>2</sup>—were accomplished as follows: the acid chloride of *d*-homopilopic acid was converted into diazomethyl *d*-homopilopoyl ketone (XII.). The action of hydrochloric acid eliminated nitrogen from the diazo-ketone with the formation of chloromethyl *d*-homopilopoyl ketone (XIII.), which with boiling alcoholic potassium phthalimide yielded phthalimido-methyl *d*-homopilopoyl ketone (XIV.). This compound on acid hydrolysis was converted into aminomethyl *d*-homopilopoyl ketone hydrochloride (XV.), which when heated with potassium thiocyanate yielded, by ring formation, 2-thiol-5-*d*-homopilopylglyoxaline (2-thiopilocarpidine) (XVI.). *d*-Pilocarpidine (XVII.) was obtained from the mercaptan by oxidation with ferric chloride, and finally methylation converted *d*-pilocarpidine into *d*-pilocarpine (XVIII.). The nitrates of these two synthetic alkaloids were found to be identical with the nitrates of the natural substances. The steps in the syntheses are shown structurally on p. 231.

The alkaloids and their acid degradation products have been synthesized by other methods and shown to be identical with the compounds from natural sources.<sup>3</sup>

<sup>1</sup> Arndt and Eistert, *Ber.*, 1935, 68, [B], 200.

<sup>2</sup> Preobrashenski, Wompe, Preobrashenski, and Schtschukina, *Ber.*, 1933, 66, [B], 1541.

<sup>3</sup> Welch, *J.*, 1931, 1370; Dey, *J.*, 1937, 1057.

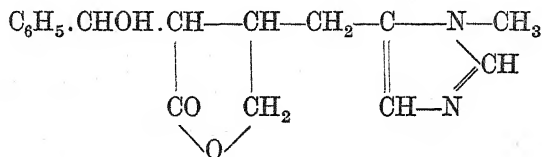


## 2. Pilosine and Pilosinine

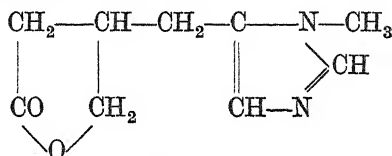
The constitution of pilosine has been investigated by Pyman.<sup>1</sup> He found that on distillation with potash solution it yields

<sup>1</sup> Pyman, P., 1912, 23, 267.

benzaldehyde and a substance called pilosinine, which closely resembles pilocarpine in physiological action. He ascribed to the two substances the following structures:—



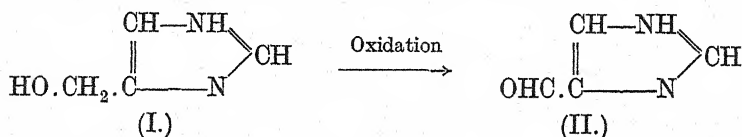
Pilosine.



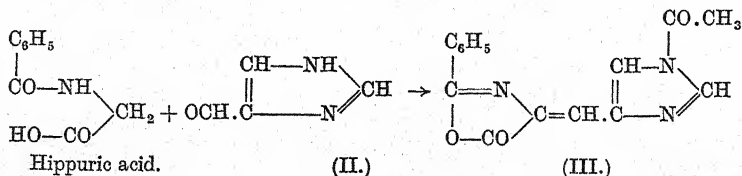
Pilosinine.

### 3. The Synthesis of Histidine

By heating together potassium thiocyanate and the hydrochloride of diamido-acetone, amido-methyl-glyoxaline mercaptan is produced; and when this is added to dilute nitric acid, it yields 4-hydroxymethyl-glyoxaline (I.), which forms the raw material of the histidine synthesis.<sup>1</sup> Oxidation with chromic acid converts it into glyoxaline formaldehyde (II.):

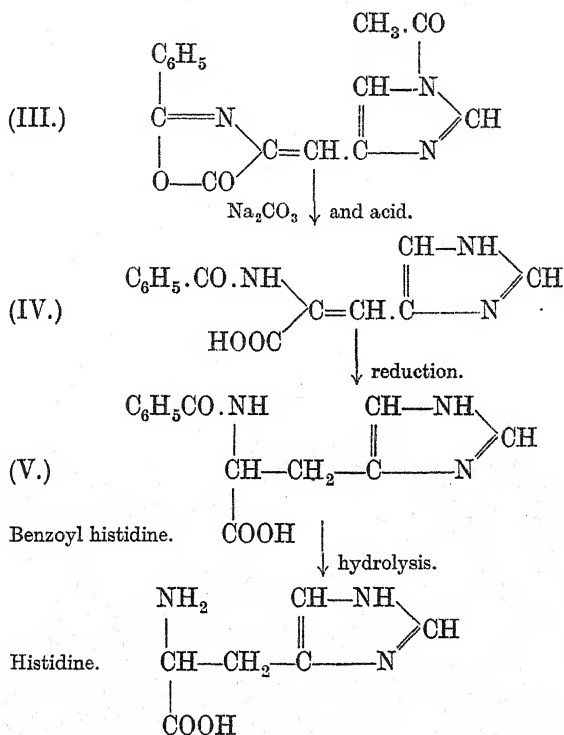


By means of acetic anhydride, the formaldehyde derivative is condensed with hippuric acid to form 2-phenyl-4-[1-acetyl-glyoxaline-4-methylidene]-oxazolone (III.):



<sup>1</sup> Pyman, J., 1916, 109, 186.

When this oxazolone derivative is boiled with very dilute sodium carbonate solution, the acetyl group is split off and the oxazolone ring opens. If, now, the calculated quantity of an acid be added, the compound (IV.) results. Reduction of this produces benzoyl-histidine (V.) from which histidine itself is obtained by hydrolysis—



### B.—THE ARECA NUT ALKALOIDS

An examination of the seeds of the betel-nut palm (*Areca Catechu*) by various workers <sup>1</sup> resulted in the discovery of five alkaloids: arecaine (also known as arecaine), arecoline, guvaine, guvacoline, and arecolidine. Another substance, <sup>2</sup> *iso*-guvaine,

<sup>1</sup> Bombelon, *Pharm. Ztg.*, 1886, 146; Jahns, *Ber.*, 1888, 21, 3404; 1890, 23, 2972; 1891, 24, 2615; *Arch. Pharm.*, 1891, 229, 669; Emde, *Apoth. Ztg.*, 1915, 30, 240; Hess, *Ber.*, 1918, 51, 1004.

<sup>2</sup> Trier, *Z. physiol. Chem.*, 1913, 85, 391; Winterstein and Weinhausen, *ibid.*, 1918, 104, 48.

has also been detected; but its identity is a matter of doubt, and suggestions have been made that it is mainly arecaidine.

Arecaidine,  $C_7H_{11}O_2N$ , furnishes a methyl ester, which is found to be identical with the alkaloid arecoline,  $C_8H_{13}O_2N$ . The formulæ of the two alkaloids can therefore be written:



The most obvious way of accounting for the group  $C_6H_{10}N$  is to assume that it represents a methylated tetrahydropyridine nucleus; and if this view were correct, then arecaidine would have the following structure:  $CH_3.N : C_5H_7.COOH$ . Obviously this leaves still unsettled the positions of the carboxyl group and the double bond in the tetrahydropyridine ring.

These two points were simultaneously cleared up by the complete synthesis of arecaidine devised by Wohl and Johnson.<sup>1</sup> By acting on acrolein (I.) with alcohol and hydrogen chloride,  $\beta$ -chloropropaldehyde acetal (II.) was produced. Condensation of this acetal with methylamine yielded  $\beta$ -methyl-iminodipropaldehyde tetra-ethyl-acetal (III.). The action of strong hydrochloric acid on (III.) gave rise to N-methyl- $\Delta^3$ -tetrahydropyridine-3-aldehyde (IV.). Oximation, followed by dehydration of the oxime by means of thionyl chloride, resulted in the formation of 3-cyano-N-methyl- $\Delta^3$ -tetrahydropyridine hydrochloride (V.). On hydrolysis, the acid obtained was found to be identical with arecaidine (VI.); and esterification of this acid produced arecoline, which, therefore, has the formula (VII.).

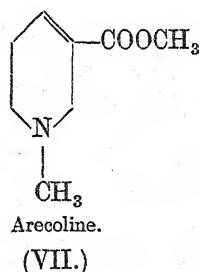
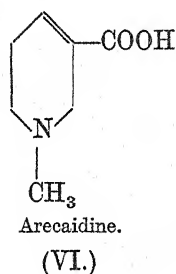
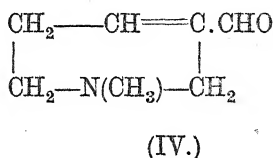
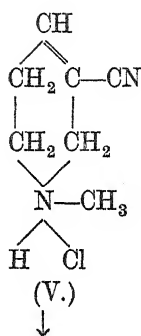
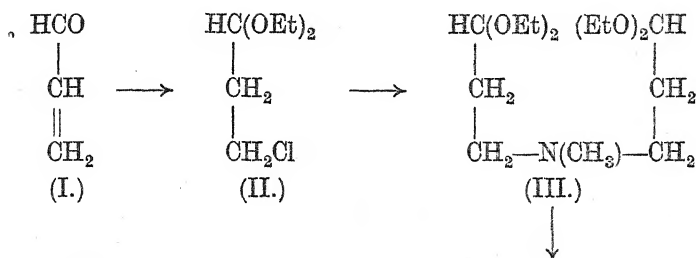
The constitution of the second pair of alkaloids, guvacine,  $C_6H_9O_2N$ , and guvacoline,  $C_7H_{11}O_2N$ , presented more difficulty than might have been expected. This, in the main, was due to Jahns, who failed to detect a carboxyl radicle in guvacine; and his results led to the view that there could be no structural kinship between guvacine and arecaidine, although the formulæ differ only by a methylene group—which naturally suggests that arecaidine might be methyl-guvacine.

This last view was taken by Trier in 1913, but was not then accepted. Five years later, Freudenberg<sup>2</sup> demonstrated that guvacine was identical with  $\Delta^3$ -tetrahydropyridine-3-carboxylic acid, which had been synthesized by Wohl and Losanitsch<sup>3</sup>

<sup>1</sup> Wohl and Johnson, *Ber.*, 1907, 40, 4712.

<sup>2</sup> Freudenberg, *Ber.*, 1918, 51, 976, 1669.

<sup>3</sup> Wohl and Losanitsch, *Ber.*, 1907, 40, 4701.



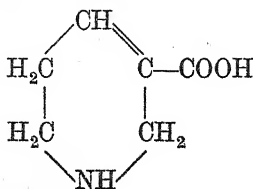
in 1907. This substance, on methylation, yields an N-methyl-derivative which proved to be identical with arecaidine; and on esterification with methyl alcohol, Wohl and Losanitsch's acid produces a methyl ester identical with guvacoline.

The formulæ for the four substances are therefore those which are shown on p. 236.

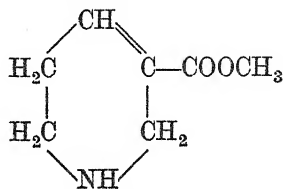
The fifth alkaloid, arecolidine,  $\text{C}_8\text{H}_{13}\text{O}_2\text{N}$ , is believed<sup>1</sup> to be 3:4-dimethoxy-1-methyl-1:2-dihydropyridine; but the evidence available is hardly sufficient to establish this formula definitely.

<sup>1</sup> Emde, *Apoth. Ztg.*, 1915, 30, 240.

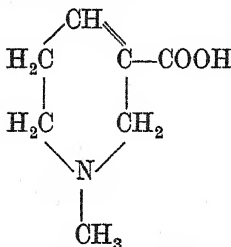




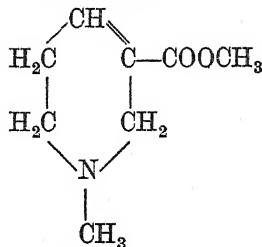
Guvacine.



Guvacoline.



Arecaidine.



Arecoline.

## C.—RICININE

The difficulties in the way of determining chemical constitution have seldom been better illustrated than in the case of this alkaloid derived from the castor bean. It has the comparatively simple composition  $C_8H_9O_2N_2$ ; yet in the course of a chequered career as a subject of investigation, it has been associated in one way or another with pyrrol, gloxaline, and pyridine; and one proposed formula even contained divalent carbon.

By heating ricinine with concentrated hydrochloric acid, Macquenne and Philippe<sup>1</sup> obtained a compound  $C_6H_7O_2N$ . Winterstein<sup>2</sup> isolated a base  $C_7H_9O_2N$ , by heating ricinine with 57.4 per cent. sulphuric acid to 140° C. When ricinine is treated with dilute potassium carbonate solution, it yields ricininic acid; and from this, by oxidation with chromic acid and dilute sulphuric acid, Böttcher<sup>3</sup> obtained methylamine, oxalic acid, and hydrocyanic acid. These three reactions form the keys to the ricinine constitution.

Since the two compounds  $C_6H_7O_2N$  and  $C_7H_9O_2N$  differ from each other by  $CH_2$ , it seemed probable that the second is the

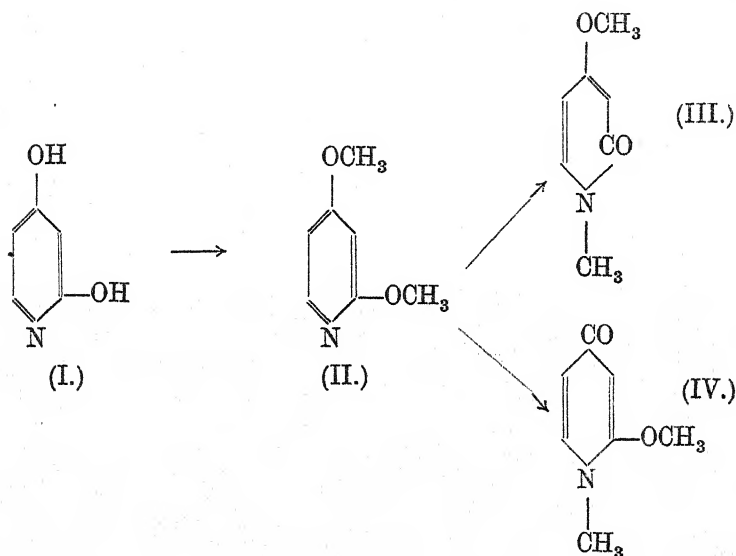
<sup>1</sup> Macquenne and Philippe, *Compt. rend.*, 1904, 138, 506; 139, 840.

<sup>2</sup> Winterstein and others, *Arch. Pharm.*, 1917, 255, 513.

<sup>3</sup> Böttcher, *Ber.*, 1918, 51, 673.

methyl derivative of the first; and the reactions of the parent substance suggested that it was a pyridone derivative.

Späth and Tschelnitz<sup>1</sup> identified this pyridone by the synthetic method. By treating the silver salt of 2:4-dihydroxypyridine (I.) with methyl iodide, they obtained the dimethyl ether (II.). On further treatment with methyl iodide, this yielded a substance which must be either 4-methoxy-1-methyl-1:2-dihydropyrid-2-one (III.) or 2-methoxy-1-methyl-1:4-dihydropyrid-4-one (IV.).

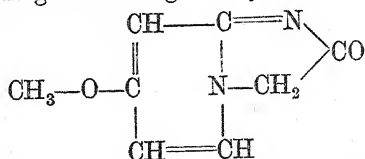


This synthetic substance proved to be identical with the compound  $C_7H_9O_2N$  derived from ricinine; and on demethylation it yielded a parent substance identical with the ricinine derivative  $C_6H_7O_2N$ . In this way the main skeleton of the ricinine molecule is established, since it must contain either the grouping (III.) or (IV.), and these differ only in the position of a methyl radicle.

At this point Späth was apparently misled by some analogies drawn by Böttcher between ricinine and histidine on the strength of the Weidel reaction, the ferric chloride colour, and a liberation of hydrocyanic acid during an oxidation with chromic and

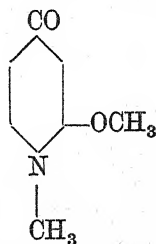
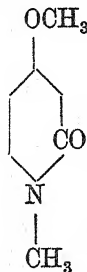
<sup>1</sup> Späth and Tschelnitz, *Monatsh.*, 1921, 42, 251.

sulphuric acid which he had carried out. Späth therefore suggested that the remaining part of the ricinine molecule was a glyoxaline ring which might be joined on as shown below :

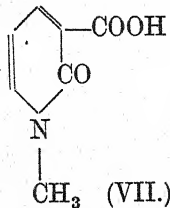
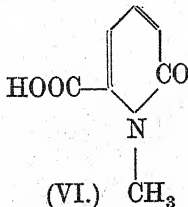
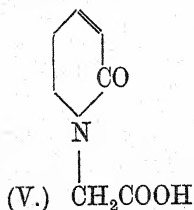


Further investigation by Späth and Koller<sup>1</sup> showed that the glyoxaline hypothesis was erroneous. Böttcher had found that on treatment with potassium hydroxide, ricinine was converted into a so-called ricinic acid. On treating this substance with phosphorus oxychloride, Späth and Koller found that it yielded a compound  $C_7H_5ON_2Cl$ , which corresponds to a replacement of one hydroxyl group by a chlorine atom. On reducing this chlorine compound by means of hydrogen and palladized barium sulphate, a substance was obtained which was termed ricinidine, having the composition  $C_7H_6ON_2$ . That this body was a nitrile is shown by its hydrolysis to a carboxylic acid  $C_7H_7O_3N$ .

Now in view of the fact that ricinine must contain either of the skeletons :



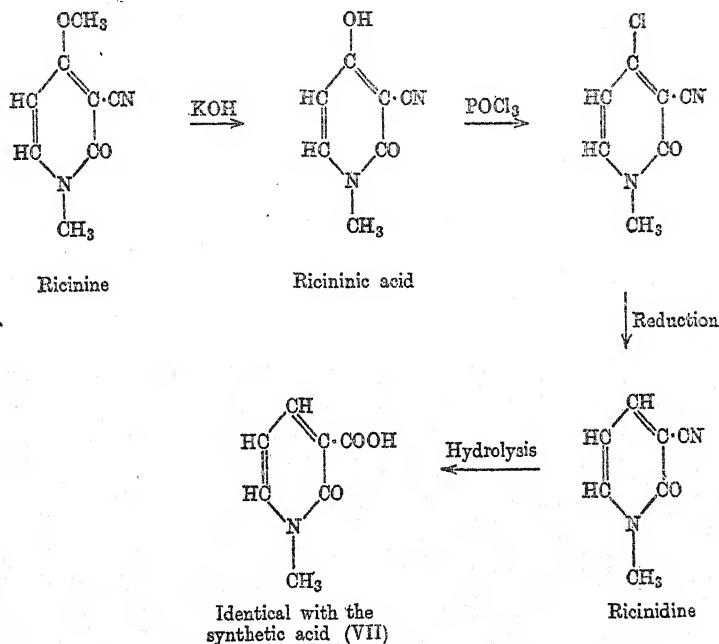
it is clear that there are only three possible carboxylic acids derivable from it in the manner described.



<sup>1</sup> Späth and Koller, *Ber.*, 1923, 56, 880.

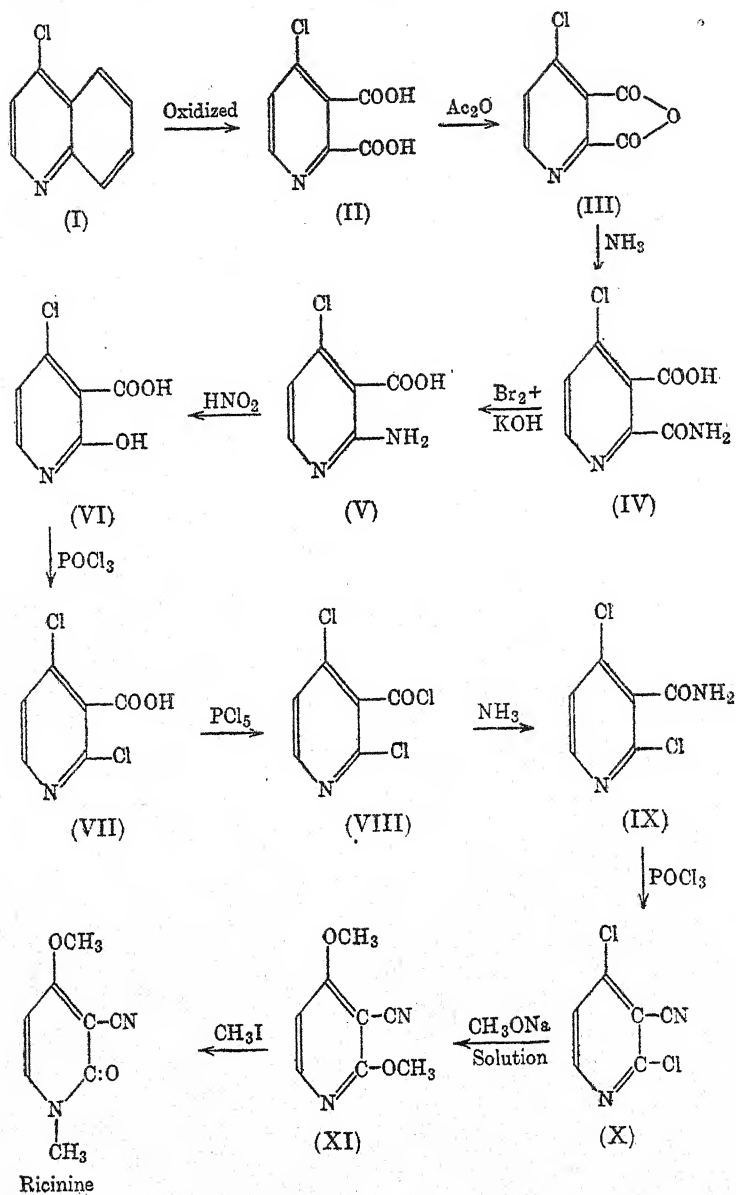
Späth and Koller synthesized all three; and it was found that the one corresponding to the structure (VII.) was identical with the acid  $C_7H_7O_3N$  derived from ricinine.

This fixes the position of the carboxyl group in the acid, and hence establishes the position of the corresponding nitrile group in ricinidine and ricininic acid; so that the reactions mentioned above can be formulated as follows:—



Ricinine has been synthesized by Späth and Koller<sup>1</sup> in the following manner. By oxidizing the chloroquinoline (I.) with potassium permanganate, the di-carboxylic acid (II.) is obtained. This is converted, by treatment with acetic anhydride, into the anhydride (III.), from which the amide (IV.) is prepared and converted by Hofmann's reaction into the amine (V.). Treatment of this amine with nitrous acid produces the hydroxy-compound (VI.) from which, by successive treatment with phosphorus oxychloride and phosphorus pentachloride, the derivatives (VII.) and (VIII.) are made.

<sup>1</sup> Späth and Koller, *Ber.*, 1923, 56, 2454.



The acyl chloride (VIII.), with ammonia, gives the amide (IX.); and this is converted into the nitrile (X.) by means of phosphorus oxychloride. This nitrile, when boiled with a solution of sodium methylate in methyl alcohol, was changed into the dimethoxy-derivative (XI.). The final step was the conversion of (XI.) into ricinine, which was accomplished by heating with methyl iodide in an evacuated tube at 120°-130° C.

The constitution of the hydroxy-acid (VI.) was proved by reducing it with hydrogen and palladized barium sulphate to 2-hydroxypyridine-3-carboxylic acid and hence to 2-hydroxypyridine. This establishes the positions of the carboxyl and hydroxyl radicles, since the 4-position is originally occupied by a chlorine atom. From this evidence, there can be no doubt as to the constitution of the compound (XI.); and since it has already been proved by earlier work that the methoxy group of ricinine is in the 4-position, the constitution of the alkaloid is now beyond dispute.

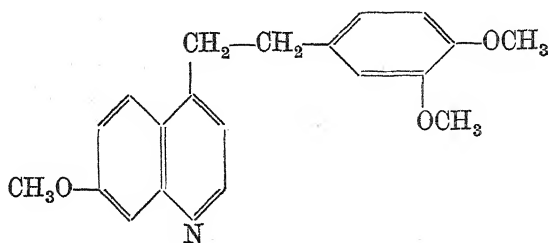
#### D.—THE ANGOSTURA ALKALOIDS

The two principal alkaloids found in cusparia or angostura bark are cusparine,  $C_{19}H_{17}O_3N$ , and galipine,  $C_{20}H_{21}O_3N$ . More recently, a third alkaloid, galipoline, has been obtained. A fourth supposed component, galipidine, is now believed to be identical with galipine; and the existence of cusparidine is doubtful.

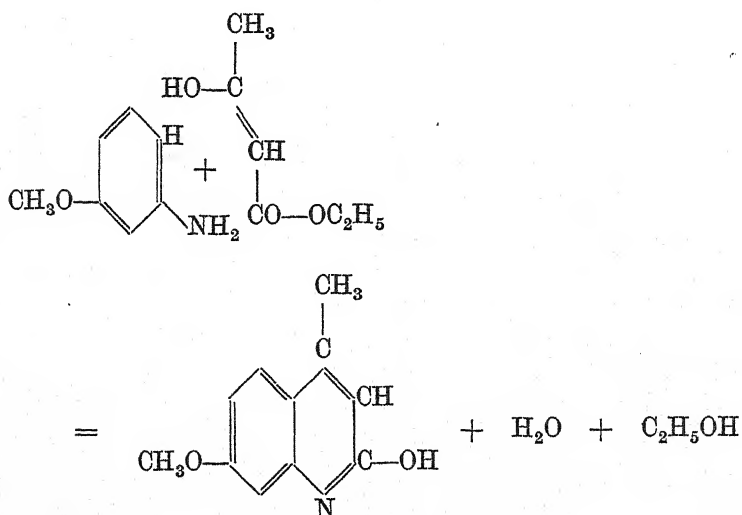
Troeger<sup>1</sup> and his collaborators observed that on oxidation galipine yielded a carboxylic acid. On demethylating this and heating the product, carbon dioxide was lost, and a substance  $C_9H_7ON$  was obtained, which on heating with zinc dust yielded quinoline. The original carboxylic acid is therefore a derivative of a methoxy-quinoline. Further, among the galipine oxidation products he believed that he had detected anisic acid and veratric acid; and on this basis he assumed that galipine must contain (1) a quinoline nucleus with (2) a methoxy-group in the 7-position (to account for his anisic acid) and (3) a veratryl

<sup>1</sup> Troeger and others, *Arch. Pharm.*, 1914, 252, 459; 1920, 258, 250.

complex attached to some point of the quinoline ring (to account for his veratric acid). On the basis of this and other evidence, he attributed to galipine the structure :



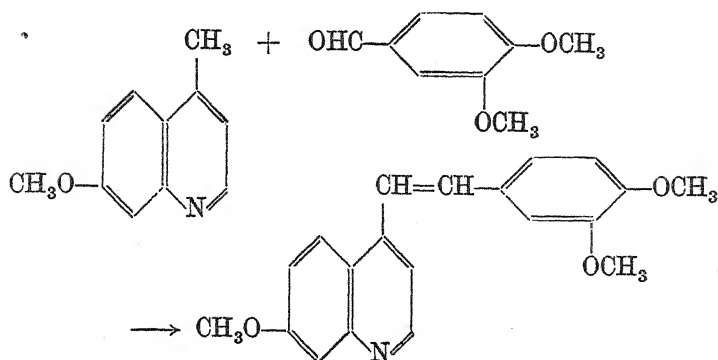
Späth and Brunner<sup>1</sup> tested this by synthesis in the following way. Acetoacetic ester was condensed with *m*-methoxyaniline



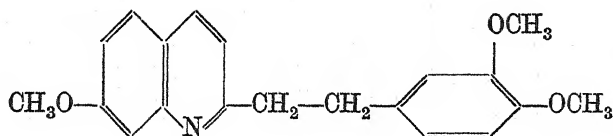
and the product was converted into 2-chloro-7-methoxy-4-methylquinoline; and thence, by reduction, into 7-methoxy-4-methylquinoline. This last substance was condensed with 3:4-dimethoxy-benzaldehyde by means of zinc chloride :

<sup>1</sup> Späth and Brunner, *Ber.*, 1924, 57, 1243.





and on reduction the product yielded a substance with a structure identical with Troeger's proposed formula for galipine. Since the synthetic material had properties different from natural galipine, Troeger's formula was proved to be incorrect. By a somewhat analogous synthesis it was shown that a compound with the structure



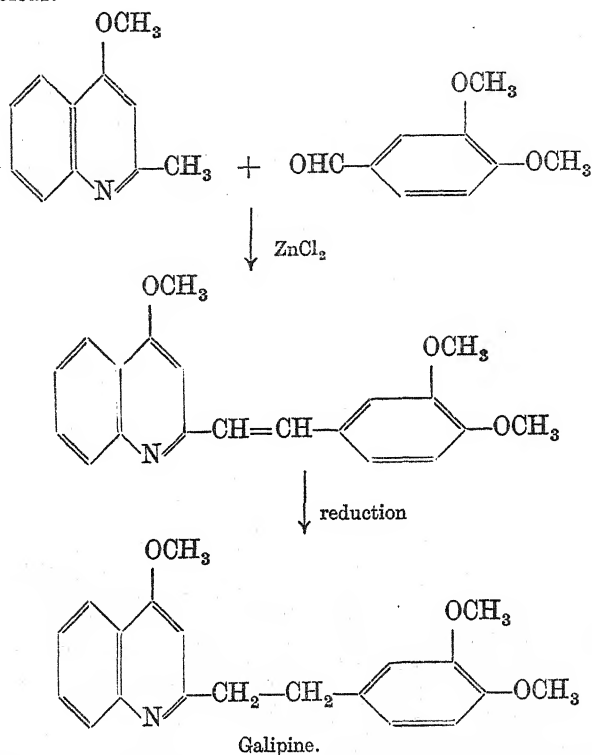
was not identical with galipine.

These results suggest that the methoxy-group of galipine is not situated in the benzenoid ring at all; and a further hint of this was obtained when it was recalled that the methyl iodide addition product of galipine easily changes into a methylgalipine. This behaviour is analogous to the change of  $\alpha$ - or  $\gamma$ -methoxyquinolines into N-methylquinolines, which makes it probable that the methoxy-radicle of galipine is really in the pyridine portion of the structure.

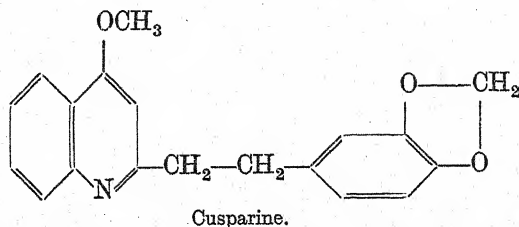
Following this line of thought, Späth and Eberstaller<sup>1</sup> synthesized galipine in the following manner. Veratryl aldehyde was condensed with 4-methoxy-2-methylquinoline by heating with zinc chloride. The product was reduced by means of hydrogen and palladized charcoal and was found to be identical with

<sup>1</sup> Späth and Eberstaller, *Ber.*, 1924, 57, 1687.

natural galipine. The formulæ below will make the various steps clear.



By an exactly similar condensation and reduction, cusparine was obtained<sup>1</sup> from 4-methoxy-1-methylquinoline and piperonal; so that its structure is therefore



As galipine has the composition  $\text{C}_{20}\text{H}_{21}\text{O}_3\text{N}$ , whilst the alkaloid galipoline<sup>2</sup> has the formula  $\text{C}_{19}\text{H}_{19}\text{O}_3\text{N}$ , it appears

<sup>1</sup> Späth and Brunner, *Ber.*, 1924, 57, 1243.

<sup>2</sup> Späth and Papaioanou, *Monatsch.*, 1929, 52, 129.

probable that galipine is a methylated galipoline. This idea is confirmed by the fact that galipoline, on methylation, yields galipine; but as there are three methoxy-groups in galipine, this reaction does not indicate the position of the unmethylated hydroxyl group in the galipoline structure. The matter has now been settled by the synthesis of galipoline, on lines analogous to those indicated in the case of the other alkaloids; and it has been shown that the hydroxyl group of the galipine quinoline nucleus is free in galipoline. This alkaloid is therefore 4-hydroxy-2-β-3': 4'-dimethoxyphenylethylquinoline.

#### E.—THE ANHALONIUM OR CACTUS ALKALOIDS

No fewer than nine alkaloids have been identified as cactus products:

Hordenine (anhaline) . . . . .	$C_{10}H_{15}ON$
Mezcaline . . . . .	$C_{11}H_{17}O_2N$
Anhalamine . . . . .	$C_{11}H_{15}O_3N$
Anhalonidine . . . . .	$C_{12}H_{17}O_3N$
Pellotine. . . . .	$C_{13}H_{19}O_3N$
Anhalonine . . . . .	$C_{12}H_{15}O_3N$
Lophophorine . . . . .	$C_{13}H_{17}O_3N$
Anhalinine . . . . .	$C_{12}H_{17}O_3N$
Anhalidine . . . . .	$C_{12}H_{17}O_3N$

The earlier work on the subject was carried out by Heffter<sup>1</sup> and it was known that the bases had a close chemical kinship with each other. In physiological action, also, they show marked resemblances.<sup>2</sup> From the latter standpoint, the most interesting is mezcaline, derived from so-called "Mezcal Buttons" (the buds of *Anhalonium Lewinii*), as it has the power of producing wonderful colour visions when used as a drug.

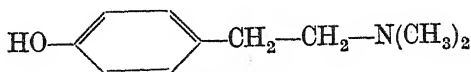
As will be seen immediately, the anhalonium alkaloids not only form a group which is interesting in itself, but in addition they throw some light upon the relationships between the normal cyclic alkaloid type and those open-chain nitrogen derivatives which possess physiological action entitling them to membership of the alkaloidal class.

<sup>1</sup> Heffter, *Ber.*, 1894, 27, 2975; 1896, 29, 216; 1898, 31, 1193; 1901, 34, 3004.

<sup>2</sup> Mogilewa, *Arch. expt. Path. Pharmac.*, 1903, 49, 137.

1. *Hordenine*

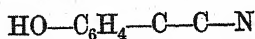
The simplest of the anhalonium alkaloids is hordenine,  $C_{10}H_{15}ON$ . Originally termed anhaline, this substance was later found to be identical<sup>1</sup> with the known compound hordenine<sup>2</sup> which is present in sprouted barley, and which has been identified as *p*-hydroxyphenyldimethylethylamine:



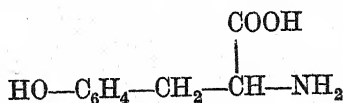
Hordenine.

Since hordenine is the dimethyl derivative of *p*-hydroxyphenylethylamine, it might be supposed that the latter would be used as a starting-point in the hordenine synthesis. Owing, however, to the readiness with which hordenine, when formed, passes into the tetra-alkyl ammonium salt form, it is found better to set out from phenylethyl alcohol. This substance is converted into the corresponding chloride which, when treated with dimethylamine, yields the base  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$ . The missing hydroxyl radicle in the *para*-position is introduced by nitration, reduction, and diazotization in the usual manner. Another method consists in the methylation of *p*-methoxyphenylethylamine followed by the action of hydriodic acid which splits off the methyl radicle of the methoxy-group.

The interest of the hordenine structure extends far beyond the constitution of a single alkaloid. Inspection shows that it contains the same skeleton as tyrosine:



Hordenine skeleton.



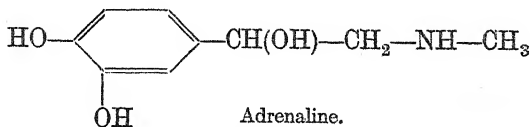
Tyrosine.

and as tyrosine is a common product in the decomposition of proteins, it seems evident that natural hordenine has a protein origin. Further, the hordenine skeleton is found in various

<sup>1</sup> Späth, *Monatsch.*, 1919, 40, 129.

<sup>2</sup> Léger, *Compt. rend.*, 1906, 142, 108; 143, 234, 916.

alkaloidal structures, as an examination of the adrenaline formula will show at a glance :



A somewhat analogous structure is traceable in papaverine, laudanosine, narcotine, hydrastine, and berberine; whilst narceine contains the chain of phenyldimethylethylamine complete. These relationships, taken in conjunction with the tyrosine formula, are obviously capable of furnishing food for interesting speculations with regard to the genesis of the alkaloids.

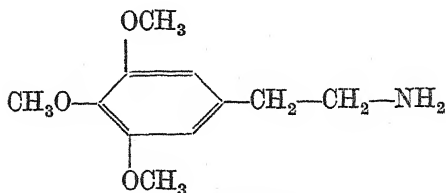
With regard to the effect of structure upon physiological properties, it is interesting to note that the conversion of the alcohol adrenaline into the ketone adrenalone does not destroy the physiological activity; nor is the presence of the methyl radicle attached to the nitrogen atom essential. One hydroxyl radicle in the benzene nucleus appears to be sufficient. A marked influence is exerted by the introduction of a methyl radicle in the  $\alpha$ - or  $\beta$ -position; for compounds containing this grouping are much less active than the parent substances.

## 2. Mezcaline

The second anhalonium alkaloid, mezcaline, has been synthesized<sup>1</sup> in the following manner, which establishes its constitution beyond doubt. Gallic acid is methylated by means of methyl sulphate. The trimethoxygallic acid so formed is converted into the acyl chloride by means of phosphorus pentachloride; and this acyl chloride is then reduced by means of hydrogen and palladized barium sulphate with the production of trimethoxybenzaldehyde. On treatment with nitromethane in the ordinary way, this aldehyde yields the corresponding nitrostyrene:  $(\text{CH}_3\text{O})_3\text{C}_6\text{H}_2\cdot\text{CH}:\text{CH}\cdot\text{NO}_2$ . Reduction of this compound proceeds in two stages, the oxime being formed first

<sup>1</sup> Späth, *Monatsh.*, 1919, 40, 129.

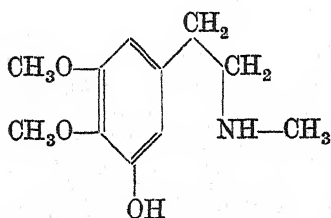
and then the amine of the structure shown below, which has been proved to be identical with mezcaine :



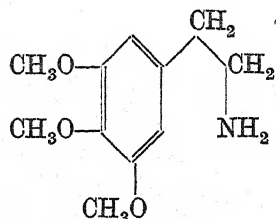
Mezcaine.

### 3. Anhalamine

Owing to certain superficial resemblances between mezcaine and anhalamine it was at first supposed that they were built up on the same skeleton. Anhalamine being a secondary base, it seemed possible that it had a formula of this type :



Anhalamine.

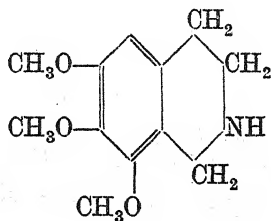


Mezcaine.

wherein one of the carbon atoms of mezcaine has been transferred from the oxygen to nitrogen. This view was disproved in the following manner. Both anhalamine and mezcaine were further methylated, an extra methyl radicle being introduced in each case. On the foregoing assumption, this operation should convert both of them into the same trimethoxy-N-methyl derivative. In practice, however, the methylation led to the production of two different compounds. Further, when the methyl-anhalamine thus formed was oxidized, no trace of trimethylgallic acid,  $(\text{CH}_3\text{O})_3\text{C}_6\text{H}_2\text{COOH}$ , could be detected among the oxidation products. This establishes definitely the fact that trimethyl-anhalamine does not contain the simple skeleton  $(\text{CH}_3\text{O})_3\text{C}_6\text{H}_2\text{C}$ . It therefore cannot be like mezcaine to this extent.

The only other plausible suggestion is that the anhalamine secondary nitrogen atom forms part of a reduced pyridine ring: in other words, that anhalamine is a tetrahydroisoquinoline derivative. But the formation of an isoquinoline ring demands an extra carbon atom in addition to the side-chain of mezcaline, as can be seen from the formula above. Since mezcaline and anhalamine both contain eleven carbon atoms, then, if the resemblance between the alkaloids is to be retained at all, this extra carbon atom can be obtained only by the demethylation of one of the mezcaline methoxy-groups.

This reasoning leads to the conclusion that anhalamine is a tetrahydroisoquinoline with one hydroxyl and two methoxyl groups in the benzenoid portion of the molecule. Now when mezcaline is treated with formaldehyde, it yields an isoquinoline derivative which must obviously have the structure:



This substance, on treatment with *m*-nitrobenzoyl chloride, yields an *N-m*-nitrobenzoyl derivative; and this last compound is found to be identical with the corresponding *N-m*-nitrobenzoyl derivative of methylanhalamine. This proves that the oxygen atoms in mezcaline and anhalamine are attached to corresponding carbon atoms; so that anhalamine is a pyrogallol derivative like mezcaline.

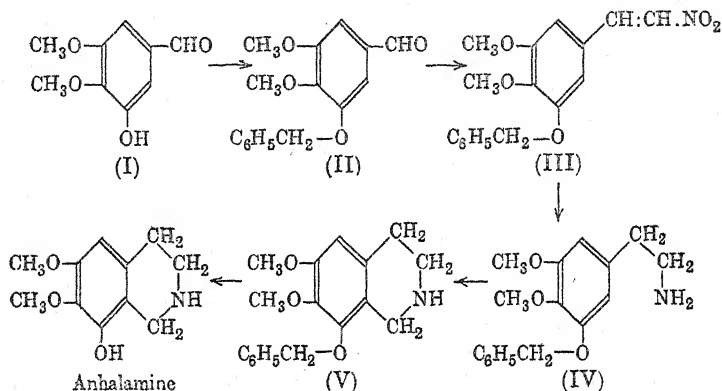
Which pair of the pyrogallol hydroxyl groups has been methylated in anhalamine remained to be settled; and this has been done by synthesis.<sup>1</sup>

The compound 5-hydroxy-3:4-dimethoxybenzaldehyde (I.) was benzylated, yielding (II.), whereby the hydroxyl group is shielded by the easily removable benzyl radicle. This substance was then condensed with nitromethane in the usual way, whereby (III.) was formed. On reduction this gave the amine (IV.)

<sup>1</sup> Späth and Röder, *Monatsch.*, 1922, 43, 93.

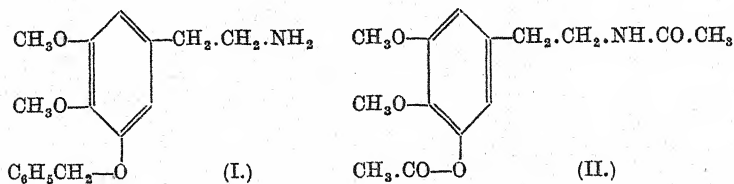


which was then condensed with formaldehyde to give the tetrahydroisoquinoline derivative (V.). On digestion with hydrochloric acid, the benzyl group was split off, the hydroxyl group being regenerated. The product was found to be identical with anhalamine.



#### 4. Anhalonidine and Pellotine

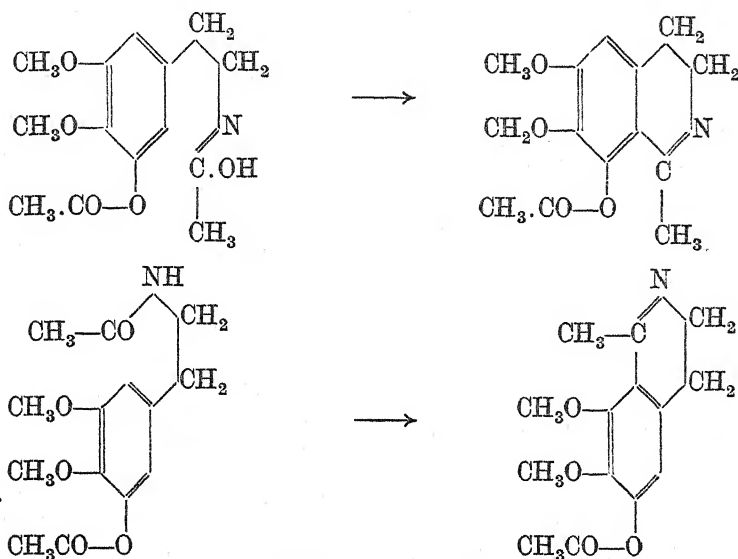
The synthesis of anhalonidine<sup>1</sup> has been achieved; but the method employed left a choice open between two possible formulæ for the alkaloid. The 5-benzyloxy-3:4-dimethoxyphenylethylamine (I.) described above was treated with hydrochloric acid, whereby the benzyl radicle was removed. Acetic anhydride converts the product into the O—N-diacetyl derivative (II.).



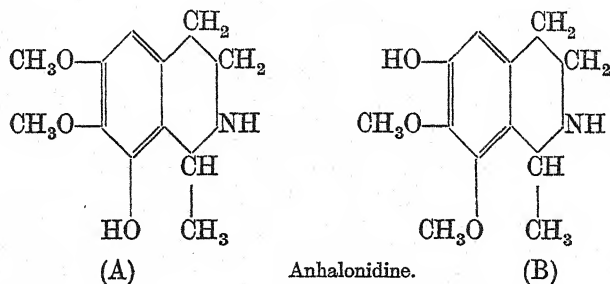
On heating (II.) with phosphorus pentoxide in toluene solution,

<sup>1</sup> Späth, *Monatsch.*, 1923, 43, 477.

a base was formed which may obviously have either of two constitutions, as shown in the formulæ below :



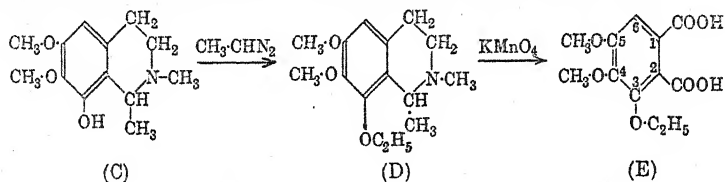
On reducing the base with tin and hydrochloric acid, a compound is produced which is identical with anhalonidine. Anhalonidine must therefore have a structure corresponding to either (A) or (B) below.



Pellotine has been shown to be the N-methyl derivative of anhalonidine. By methylating the above-mentioned dihydroisoquinoline compound before reduction with tin and hydrochloric acid, and then carrying out the reduction as before, it is possible to obtain pellotine.<sup>1</sup>

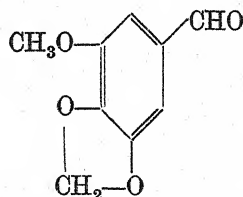
<sup>1</sup> Späth, *Monatsch.*, 1923, 43, 477.

The further examination of pellotine permitted a choice to be made between the two structures (A) and (B) for anhalonidine. When pellotine was transformed by the action of diazoethane into the ethyl ether (D) and then oxidized with potassium permanganate the product isolated was 4:5-dimethoxy-3-ethoxyphthalic acid (E).<sup>1</sup> Since pellotine is the N-methyl derivative of anhalonidine it follows that the latter must be given the structure (A) and pellotine the corresponding structure (C).

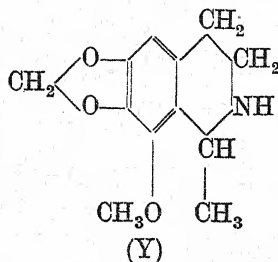
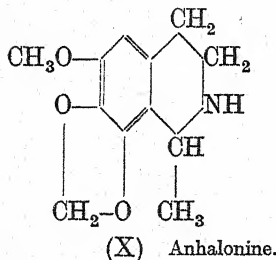


### 5. Anhalonine and Lophophorine

Späth and Gangl<sup>2</sup> synthesized anhalonine by a method quite analogous to that described above in the case of anhalamine with the exception that instead of hydroxydimethoxybenzaldehyde they began with the substance which they obtained by the



ozonization of myristicine. This aldehyde was condensed with nitromethane, and the product subjected to reduction, acetylation, and dehydration. The result must be a compound having either formula (X) or formula (Y).

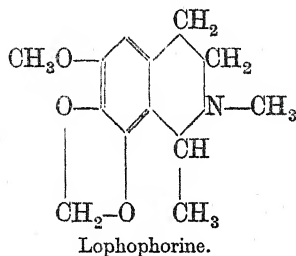


<sup>1</sup> Späth and Passl, *Ber.*, 1932, 65, [B], 1778.

<sup>2</sup> Späth and Gangl, *Monatsch.*, 1923, 44, 103.

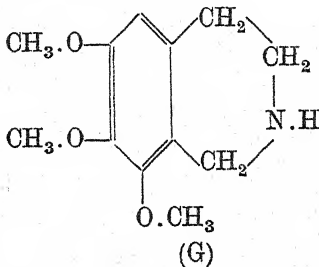
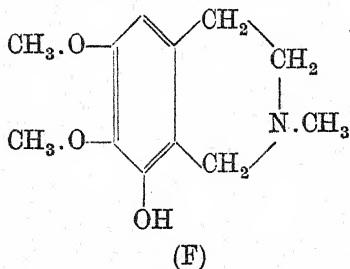
Now a compound corresponding to the N-methyl derivative of the formula (Y) was synthesized by means of magnesium methyl iodide and cotarnine; and this body proved to be different from the N-methyl derivative of anhalonine. The structure of anhalonine must therefore correspond to formula (X) given above.

Lophophorine has been shown by Späth to be identical with the N-methyl derivative of anhalonine, so that its structure is obviously that which is derived from the anhalonine formula:



#### 6. Anhalidine and Anhalinine

Anhalidine is N-methylanhalamine, as methylation of the latter with methyl iodide in methyl alcohol followed by treatment with sodium carbonate leads to a compound (F) identical with natural anhalidine.<sup>1</sup> Anhalinine has been shown by synthesis to be 6:7:8-trimethoxy-1:2:3:4-tetrahydroisoquinoline (G).<sup>2</sup>

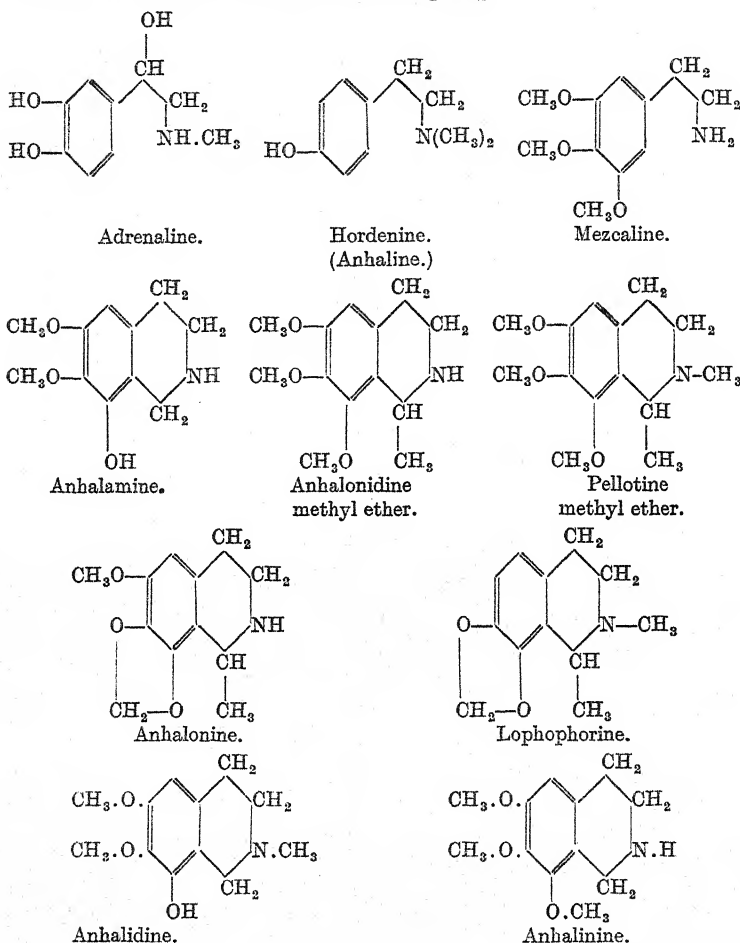


The formulæ of the complete series of alkaloids (or methyl ethers of known constitution), as well as that of adrenaline, are

<sup>1</sup> Späth and Becke, *Ber.*, 1935, 68, [B], 944.

<sup>2</sup> *Idem*, *ibid.*, 1935, 68, [B], 501.

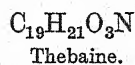
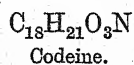
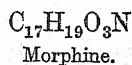
given below so as to bring out the resemblances in structure between the various members of the group.



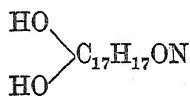
#### F.—THE PHENANTHRENE GROUP

##### 1. *The Relations between Morphine, Codeine, and Thebaine*

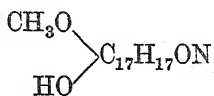
The general resemblance between morphine, codeine, and thebaine can be seen by the comparison of their compositions :



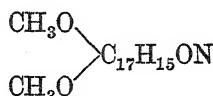
Morphine contains two hydroxyl groups, one of which is phenolic,<sup>1</sup> while the other is an alcoholic radicle.<sup>2</sup> When morphine is methylated, codeine is formed, which has no phenolic properties. This establishes that codeine is methylmorphine and carries its methyl radicle on the phenolic oxygen atom of morphine. The third oxygen atom in morphine and codeine is indifferent to reagents and is therefore assumed to be ethereal in character.<sup>3</sup> When subjected to Zeisel's reaction, thebaine loses two methyl radicles; so that evidently it contains two methoxyl groups. The formulæ of the three substances may therefore be written as below:—



Morphine.



Codeine.



Thebaine.

wherein the third oxygen atom is assumed to be ethereal in character.

All three alkaloids are tertiary bases and each of them contains a phenanthrene nucleus, as will be seen later.

## 2. Methylmorphimethine<sup>4</sup>

I. Codeine unites directly with one molecule of methyl iodide, forming codeine-methyl-ammonium iodide. When this compound is boiled with caustic soda it yields a tertiary base,  $\text{C}_{19}\text{H}_{23}\text{O}_3\text{N}$ , which is known as methylmorphimethine. The process is evidently one of exhaustive methylation,\* and the result proves that in codeine the nitrogen atom forms part of a ring.

II. When methyl iodide is allowed to unite with methylmorphimethine, a quaternary ammonium iodide is produced which can be converted into the corresponding methylmorphimethine-methyl-ammonium hydroxide in the usual way. On heating, this hydroxide decomposes; and among the products

<sup>1</sup> Matthiessen and Wright, *Proc. Roy. Soc.*, 1869, 17, 364.

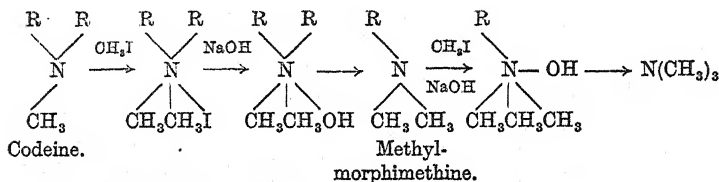
<sup>2</sup> Hesse, *Annalen*, 1884, 222, 203.

<sup>3</sup> Vongerichten, *Annalen*, 1882, 210, 105.

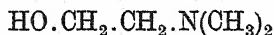
<sup>4</sup> Knorr, *Ber.*, 1889, 22, 182.

\* See Vol. I., p. 248.

trimethylamine is found. This proves that the nitrogen atom in methylmorphimethine-methyl-ammonium hydroxide is attached to three methyl radicles. Now since only one methyl group was introduced into the molecule in Stage I. and a second one in Stage II. it follows that the third methyl radicle must have been attached to the original nitrogen atom in codeine. Codeine, therefore, contains a nitrogen atom attached by two of its valencies to a cyclic grouping, whilst the third valency holds a methyl radicle. The course of the various reactions may be symbolized as follows, RR being used to represent the remainder of the codeine structure :



III. When treated with acetic anhydride,<sup>1</sup> methylmorphimethine yields hydroxyethyltrimethylamine :



This chain might have been attached to the parent molecule either by the intermediation of the oxygen atom or of a carbon atom. By actual synthesis of the ether type of compound from the decomposition products,<sup>2</sup> it was proved that this structure was not the one sought ; so that the side-chain is not attached to the rest of the codeine molecule by means of the oxygen atom. The linkage is therefore one between two carbon atoms ; and the oxygen atom of hydroxyethyltrimethylamine is not part of the original molecule, but is supposed to appear as the result of a reaction between water and the primary decomposition product : a vinyl derivative.\*

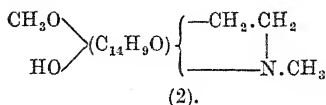
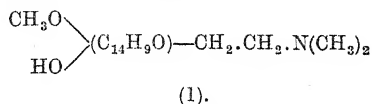
<sup>1</sup> Knorr, *Ber.*, 1889, 22, 181, 1113 ; 1894, 27, 1144 ; Knorr and Smiles, *ibid.*, 1902, 35, 3009.

<sup>2</sup> *Ibid.*, 1905, 38, 3143.

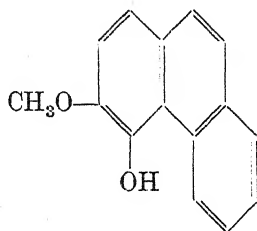
\* The primary product is assumed to be  $\text{CH}_2 : \text{CH} \cdot \text{N}(\text{CH}_3)_2$  which is then supposed to add on a molecule of water at the double bond.



IV. Summarizing the information gained in the foregoing paragraphs, it is clear that methylmorphimethine may be represented by (1) while codeine corresponds to (2).



V. The second product obtained when methylmorphimethine is decomposed with acetic anhydride is a methoxyhydroxyphenanthrene which has been shown, by synthesis,<sup>1</sup> to have the structure :



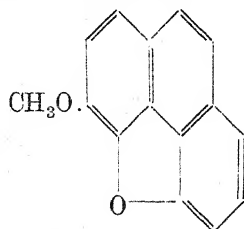
### 3. The Structures of Morphine and Codeine

I. The whole of the seventeen carbon atoms in the morphine molecule are now accounted for : since there are fourteen in the phenanthrene nucleus ; two in the ring of which nitrogen forms a member ; and one in the methyl radicle attached to the nitrogen atom. The next step is to determine, if possible, the position of the ethereal oxygen atom in the molecule. Proof has been given above that this oxygen atom does not serve to connect the nitrogen chain with the molecular nucleus ; so it evidently must be linked with two carbon atoms of the phenanthrene group. Since a ring composed of four carbon and one oxygen atom is a fairly stable one, it is concluded that this grouping occurs in morphine ; and this view is supported by evidence drawn from the effect of the Grignard reagent upon the analogous oxygen atom in thebaine,<sup>2</sup> and the production of the methyl ether of morphenol (I.) from codeine through  $\beta$ -methylmorphimethine. The structure of morphenol was demonstrated by its conversion into 3 : 4 : 5-trihydroxyphenanthrene (II.) by fusion

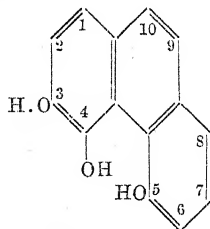
<sup>1</sup> Pschorr and Sumuleanu, *Ber.*, 1900, **33**, 1810, 1824 ; Pschorr and Vogtherr, *Ber.*, 1902, **35**, 4412.

<sup>2</sup> Freund, *Ber.*, 1903, **38**, 3234.

with potassium hydroxide,<sup>1</sup> and by the synthesis of 3:4:5-trimethoxyphenanthrene identical with the product obtained by methylating morphenol from natural sources.<sup>2</sup>

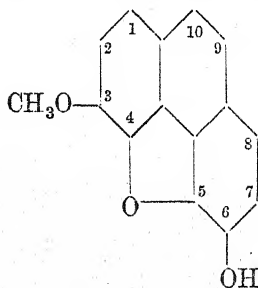


(I.)



(II.)

Morphine therefore contains the skeleton shown in (I.).



(III.)

II. The position of the remaining hydroxyl radicle has been determined in the following way. When codeine is oxidized by means of potassium permanganate or chromic acid,<sup>3</sup> it gives the corresponding ketone codeinone, the group  $-\text{CH}(\text{OH})-$  being changed to a carbonyl radicle. On treatment with acetic anhydride,<sup>4</sup> codeinone yields 3-methoxy-4,6-dihydroxyphenanthrene, which places the hydroxyl group in position 6 as shown above in the formula (III.)

III. It has now been shown that morphine contains a phenanthrene nucleus with six substituents attached to it: two places being occupied by the ends of the nitrogen ring, two by the hydroxyl groups and two by the ethereal oxygen. On counting the hydrogen atoms in this structure, it will be found

<sup>1</sup> Vongerichten and Dittmer, *Ber.*, 1906, 39, 1718.

<sup>2</sup> Pschorr *et al.*, *Annalen*, 1912, 391, 40.

<sup>3</sup> Ach and Knorr, *Ber.*, 1903, 36, 3067.

<sup>4</sup> Knorr, *Ber.*, 1903, 36, 3077.

that the total is six less than the number actually required by the formula for morphine. From this it is clear that morphine contains a partially reduced nucleus. The position of one of the reduced nuclei is indicated by the alcoholic hydroxyl in morphine; since this must be attached to a hexahydro-ring.

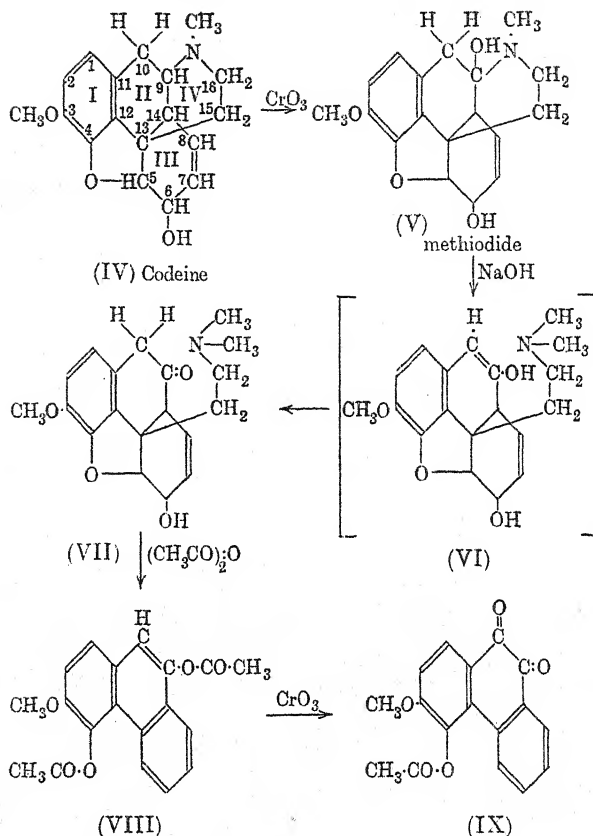
IV. The only remaining problems are the attachment of the nitrogen ring to the nucleus and the position of an ethylenic linkage. The known facts indicate clearly that the linkage of the nitrogen atom is to carbon atom 9 of the phenanthrene skeleton (II.). Thus codeine (IV.) can be oxidized by chromic acid at a low temperature to hydroxycodeine (V.), which yields a diacetyl-derivative. The new hydroxyl group of this compound is alcoholic and not phenolic in function. Treatment of the methiodide of hydroxycodeine in hot aqueous solution with sodium hydroxide converts it into ketodihydromethylmorphimethine (VII.), which forms a monoacetyl-derivative. The action of acetic anhydride splits off hydroxyethyldimethylamine,  $\text{HO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{N} : (\text{CH}_3)_2$ , from the methine, converting it into methoxydiacetoxyphenanthrene (VIII.). This substance on oxidation with chromic and glacial acetic acids yields the known 3-methoxy-4-acetoxyphenanthrene-9:10-quinone (IX.), one acetoxy group being eliminated during the change.<sup>1</sup> The structures may be formulated as shown on p. 260.

These changes can be adequately explained by assuming that the oxidation of codeine results in 9- or 10-hydroxycodeine. It is concluded that the nitrogen atom of ring IV. (see structure IV. below) is attached at this same point, as the keto-methine (VII.)

probably arises from the unsaturated grouping  $-\text{CH}=\overset{|}{\text{C}} \cdot \text{OH}$  (VI.) formed by rupture of the nitrogen ring. The unsaturated

grouping goes over to the form  $-\text{CH}_2-\overset{|}{\text{C}}\text{O}$  (VII.), and on the conversion of the keto-methine into the phenanthrene derivative (VIII.) the 9- or 10-oxygen appears again as hydroxyl. Finally, oxidation of the phenanthrene derivative to the 9:10-quinone involves the elimination of one acetoxy-group, a further indication of the presence of hydroxyl in the 9- or 10-position in the phenanthrene compound and consequently in hydroxycodeine.

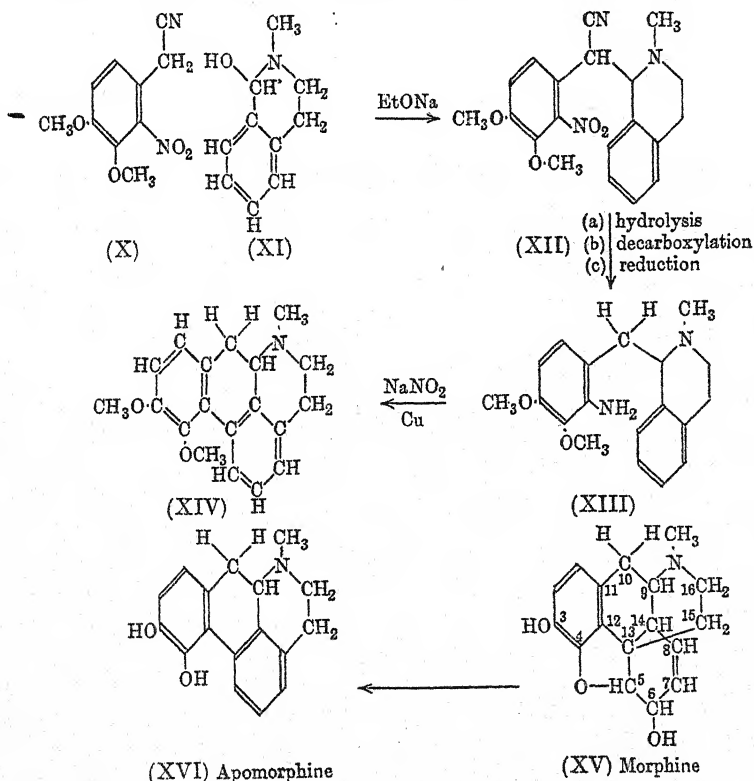
<sup>1</sup> Knorr, *Ber.*, 1903, 36, 3068; Knorr and Schneider, *ibid.*, 1906, 39, 1414; Knorr and Horlein, *ibid.*, 1902, 35, 4412; 1906, 39, 3252.



These conclusions are supported by further evidence from the structure of apomorphine. When morphine is warmed with hydrochloric acid it is converted, by the loss of one molecule of water, into apomorphine.<sup>1</sup> Although the morphine compounds readily undergo intramolecular changes it is generally agreed that the nitrogen atom retains its original attachment to the phenanthrene skeleton, except in the formation of the methylmorphimethines where the nitrogen ring is broken. This being so, if it can be proved, in spite of other changes in the molecule, that in apomorphine the nitrogen atom is attached to carbon atom 9, it may be concluded that a similar attachment exists in morphine. The structure of apomorphine has been demonstrated by two

<sup>1</sup> Vongerichten, *Ber.*, 1898, 21, 3198.

different methods of synthesis. The final stages of one of these may be given.<sup>1</sup> Molecular quantities of 2-nitro-3:4-dimethoxyphenylacetonitrile (X.) and 1-hydroxy-2-methyltetrahydroisoquinoline (XI.) were condensed in the presence of sodium ethoxide. The resulting cyanide (XII.) was hydrolysed to the acid and decarboxylated by means of boiling hydrochloric acid. The nitro-group was then reduced yielding 1-(2'-amino-3':4'-dimethoxybenzyl)-2-methyl-1:2:3:4-tetrahydroisoquinoline (XIII.). The dihydrochloride of this compound was treated with sodium nitrite and copper powder. The diazotization was accompanied by ring closure to yield dimethoxyapomorphine (XIV.). This was isolated as the methiodide and proved to be identical with the product from apomorphine (XVI.) derived from natural morphine (XV.). The structures are as follows:—



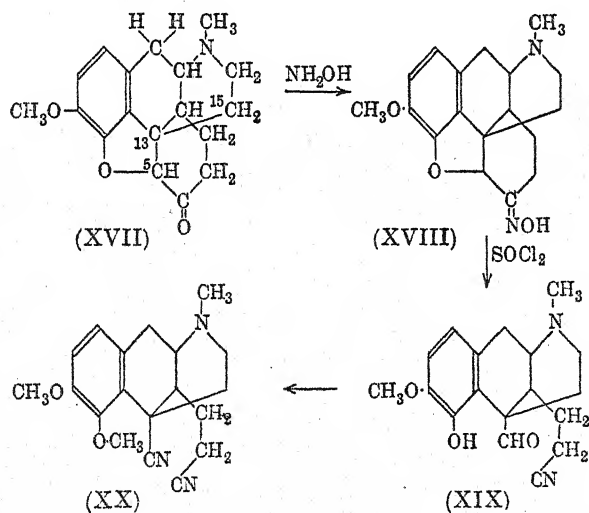
<sup>1</sup> Avenarius, Pschorr and Herz, *Ber.*, 1929, 62, [B], 321.

The point of attachment of carbon atom 15 to complete the nitrogen-containing ring (see structure IV.) has now to be settled. This has long proved a puzzle. Earlier views were that the nitrogen ring was formed by the join of carbon atom 15 to carbon atom 8 or 5. Structures such as these, however, have not proved wholly satisfactory and carbon atom 15 is now regarded as being attached to carbon atom 13. In a great number of decompositions of morphine and its related compounds a true phenanthrene and an hydroxy-ethylamine are simultaneously produced, and, moreover, this extrusion of the amino side-chain is never observed independently of the formation of the phenanthrene derivative. Thus, codeinone reacts with acetic anhydride to give 3-methoxy-4:6-diacetoxy-phenanthrene and hydroxy-ethyl-methylamine. Similarly morphine, thebaine and codeine break down with various reagents to yield a phenanthrene with the accompaniment of an ethyl-methylamine residue. This process is so common in the chemistry of morphine and its allies that its cause must be attributed to some general property of the morphine structure. It may be concluded that the formation of an aromatic phenanthrene derivative cannot take place for structural reasons unless the ethylamine side-chain is displaced in favour of a hydrogen atom or hydroxyl group. Further, if the structure given for morphine or codeine (XV. or IV.) is inspected it will be seen that the only structural arrangement which could prevent aromatic ring formation is that where the side-chain is attached to a carbon atom common to two nuclei. Carbon atoms 11 and 12 are already part of an aromatic nucleus, so that carbon atoms 13 and 14 are the only points fulfilling the condition. It will be recollected that angle methyl groups of certain terpene derivatives are extruded during the conversion into aromatic compounds.\* Applying these ideas to the morphine-codeine structure the nitrogen-containing ring should be completed by the join of carbon atom 15 to carbon atom 13 or 14. Of these two positions 13 is preferred as it permits an appropriate structure to be assigned to thebaine (XXIII.). This structure also explains the readiness with which morphine (XV.) undergoes intramolecular rearrangement to yield apomorphine (XVI.). This change involves the development of aromatic properties in ring III., and the consequent breaking of the bond between carbon

\* See Chapters V., VI. and VII.

atoms 15 and 13. In this case carbon atom 15 transfers to carbon atom 8 with the formation of a new ring.<sup>1</sup>

That carbon atom 15 of morphine is attached to carbon atom 13 rather than to carbon atom 5 receives support from the following series of changes. Dihydrocodeinone (XVII.) was converted into its oxime (XVIII.). A Beckmann change was brought about by the action of thionyl chloride yielding an *iso*-oxime (XIX.). This compound was shown to be a cyano-aldehyde. Its methyl ether was converted into the oxime and the action of thionyl chloride yielded a dinitrile (XX.) in which the nitrogen ring was still intact.<sup>2</sup> Inspection of the structures given below will make it evident that an aldehyde would not be produced but a ketone, and the formation of a dinitrile of the type described would be impossible, if carbon atom 5 carried the ethylamine side-chain.



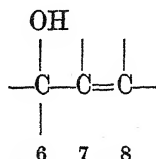
The position of the ethylene linkage in the morphine-codeine molecule has now to be fixed. Although structures for morphine containing bridged arrangements in the carbon ring III. have been seriously considered, it is now agreed that the molecule contains an ethylene linkage. Codeine can be converted with

<sup>1</sup> Gulland and Robinson, *J.*, 1923, 980; *Mem. and Proc. Manchester Lit. and Phil. Soc.*, 1924-25, 69, 79.

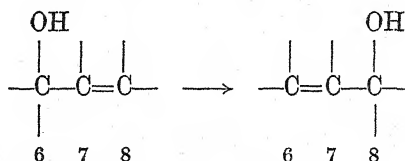
<sup>2</sup> Schöpf, *Annalen*, 1927, 452, 211.



ease into a dihydro-derivative by catalytic hydrogenation, and the action of a dilute aqueous solution of potassium permanganate leads to the addition of two hydroxyl groups.<sup>1</sup> This linkage is best placed between carbon atoms 7 and 8 of ring III. to make clear the various changes which morphine, codeine and their derivatives undergo. For example, the conversion of codeine into pseudo-codeine (XXI.) can be readily explained on this basis. Pseudo-codeine has been shown by its degradation to 3-methoxy-4:8-dihydroxyphenanthrene to have its alcoholic hydroxyl group attached to carbon atom 8 of ring III.<sup>2</sup> When the alcoholic hydroxyl group of codeine is replaced by chlorine and the resulting chlorocodeide heated with dilute acetic acid pseudo-codeine is obtained, the alcoholic hydroxyl group having been moved from carbon atom 6 to carbon atom 8. If the grouping



is present in codeine the shift is readily understood and would take place according to the scheme



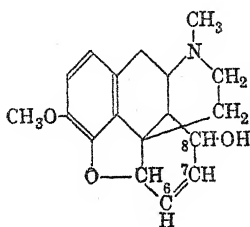
This rearrangement is analogous to the geraniol-linalool type of isomeric change.\* Similarly the isomerism of the methyl-morphimethines is explained; the  $\alpha$ -isomers correspond with codeine, having the alcoholic hydroxyl group attached to carbon atom 6 and the ethylene linkage between carbon atoms 7 and 8, the  $\epsilon$ -isomer corresponds with pseudo-codeine, and the  $\beta$ -isomer (XXII.) is considered to have the hydroxyl group at

<sup>1</sup> Wieland and Koralek, *Annalen*, 1923, 433, 267.

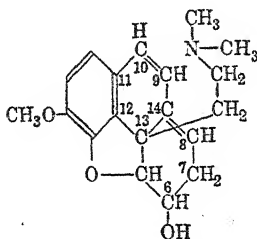
<sup>2</sup> Knorr and Horlein, *Ber.*, 1907, 40, 2042, 3341; Pschorr, Dickhäuser, and D'Avis, *Ber.*, 1912, 45, 2212.

\* See Volume I., p. 241.

carbon atom 6 and the ethylene linkage between carbon atoms 8 and 14, thus becoming conjugated with the ethylene linkage which is present in all the methylmorphimethines at position 9-10.<sup>1</sup>



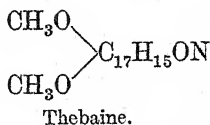
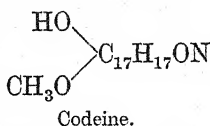
(XXI) Pseudo-codeine

(XXII)  $\beta$ -methylmorphimethine

It will be noticed that in addition to the isomers mentioned there is the possibility of stereoisomerism in these compounds. Some of these stereoisomers are known. Thus codeine on conversion into chlorocodeide and boiling with dilute acetic yields *isocodeine*. Now when codeine and *isocodeine* are oxidized with chromic acid, they yield the same codeinone, which proves them to be structurally identical but stereoisomeric on account of the arrangement of the  $-\text{CH}(\text{OH})-$  groups in space, a difference which vanishes when the secondary alcoholic radicle is oxidized to a carbonyl group.<sup>2</sup>

#### 4. Thebaine, Neopine and Sinomenine

(a) *Thebaine*.—An examination of the formulæ for codeine and thebaine

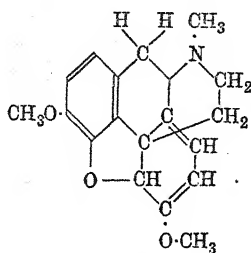


will show that thebaine apparently contains a structure similar to codeine, except that it has two hydrogen atoms less in its nucleus. It is reasonable to assume that in thebaine there is a double bond which does not exist in the codeine molecule.

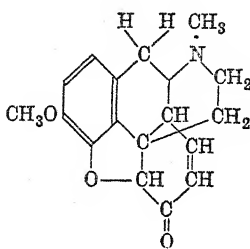
<sup>1</sup> Gulland and Robinson, *loc. cit.*

<sup>2</sup> Schryver and Lees, *J.*, 1900, 77, 1042; 1901, 79, 563; 1907, 91, 1408; Knorr and Horlein, *Ber.*, 1906, 39, 4409; 1907, 40, 3844.

When thebaine is hydrolysed with dilute acid, it yields codeinone,<sup>1</sup> a ketone also derivable from codeine by oxidation. The most satisfactory explanation of these reactions is based on the assumption that thebaine (XXIII.) is the ether derived from the enolic form of codeinone (XXIV.)—

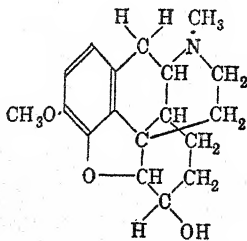


(XXIII.) Thebaine

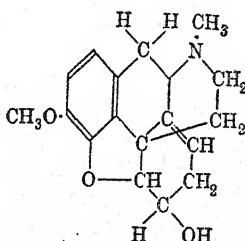


(XXIV.) Codeinone

(b) *Neopine*.—Neopine is a comparative newcomer to the opium alkaloids. It is isomeric with codeine and was shown to be identical with  $\beta$ -codeine.<sup>2</sup> It can be converted into  $\beta$ -methylmorphimethine, in which the ethylene linkage is between carbon atoms 8 and 14. When neopine was catalytically reduced it was converted into dihydrocodeine (XXV.).<sup>3</sup> The structure (XXVI.) has been allocated to it.



(XXV.)



(XXVI.) Neopine

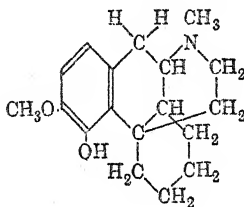
(c) *Sinomenine*.—Sinomenine is not an opium alkaloid, but is obtained from the Japanese plant *Sinomenium acutum* along

<sup>1</sup> Knorr, *Ber.*, 1906, 39, 1409; Freund, *ibid.*, 844.

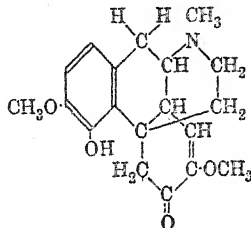
<sup>2</sup> Dobbie and Lauder, *J.*, 1911, 99, 34; Duin, Robinson, and Smith, *J.*, 1926, 903.

<sup>3</sup> Skita and Frank, *Ber.*, 1911, 44, 2865; Mannich and Löwenheim, *Arch. Pharm.*, 1920, 258, 295.

with a number of other alkaloids. In structure it is closely related to the morphine group. Its molecular structure is  $C_{19}H_{23}O_4N$ . It can be broken down to phenanthrene, and both sinomenine and its dihydro-derivative on reduction with zinc amalgam and hydrochloric acid yield tetrahydrodeoxycodine (XXVII.). From these and other properties of the substance the structure (XXVIII.) has been assigned to it.<sup>1</sup>



(XXVII.)



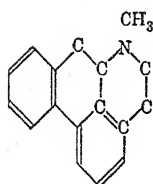
(XXVIII.) Sinomenine

### 5. The Aporphines

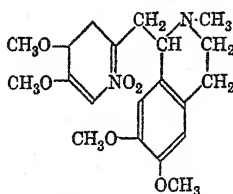
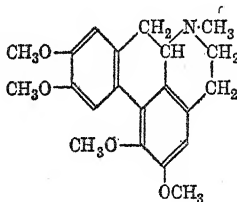
Alkaloids containing the aporphine skeleton (XXIX.) have been isolated from a variety of plants of the poppy family. Of the natural compounds, glaucine, dicentrine, bulbocapnine and isothebaine are perhaps the best known. To these may be added apomorphine obtained from morphine by intramolecular change and the loss of one molecule of water. These compounds are of interest here as they serve to show the structural connection between the morphine compounds and other *isoquinoline* alkaloids such as papaverine and laudanosine. The relationship between morphine and apomorphine has already been described (p. 260). On the other hand glaucine (XXXI.) can be readily prepared from laudanosine in the following way.

Nitration of laudanosine produces nitrolaudanosine (XXX.) which is then reduced to aminolaudanosine. This last substance is then diazotized; and when the diazo-derivative is heated with copper powder, racemic glaucine (XXXI.) is formed, which can be resolved into optical antipodes by means of tartaric acid.

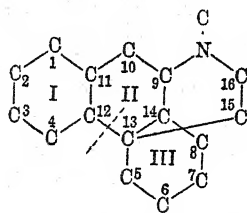
<sup>1</sup> Ishiwari, *Chûgai Iji Shimpô*, 1920, 959, 1; Kondo and Ochiai, *Annalen*, 1929, 470, 224; Goto, *Proc. Imp. Acad. Tokyo*, 1926, 2, 7, 167, 414.



(XXIX.)

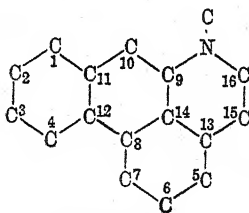
(XXX.)  
Nitrolaudanosine(XXXI.)  
Glaucine

When the skeleton structures of morphine and papaverine are compared it will be noticed that if the bond between carbon atoms 12 and 13 of the morphine structure (XXXII.) is broken and ring III. rotated through  $180^\circ$ , about the axis carbon atoms 6 and 14, the papaverine skeleton is obtained, and if carbon atoms 8 and 12, now in juxtaposition, are joined, the aporphine ring system is formed (XXXIII.).



(XXXII.) Morphine

(a) rupture of  
bond 12-13  
(b) rotation of  
ring III



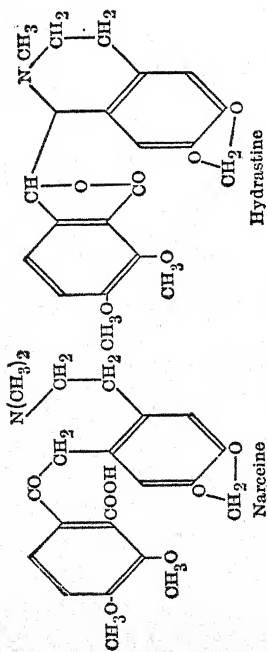
(XXXIII.)

## 6. The Relations between the Isoquinoline and Phenanthrene Alkaloids

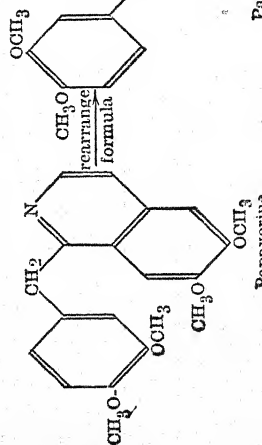
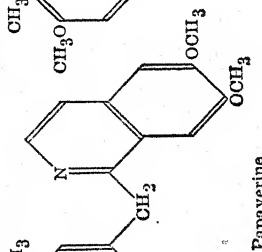
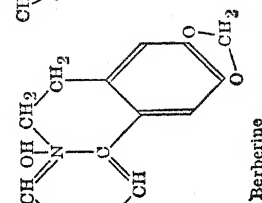
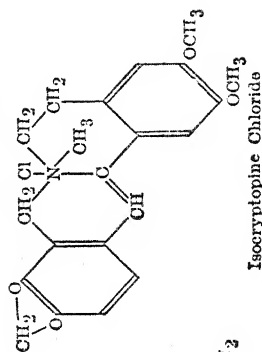
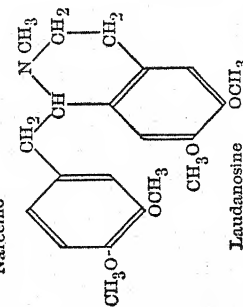
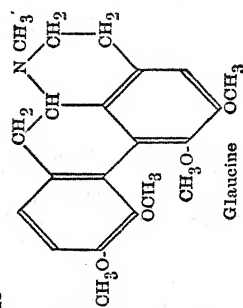
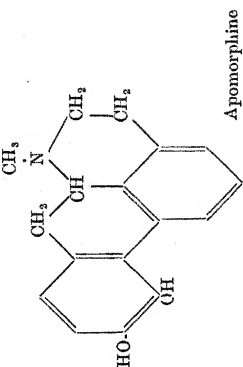
There are certain similarities in the structures of the *iso*-quinoline and phenanthrene alkaloids which are apt to be overlooked when the various substances are considered individually. and it seems advisable to point out here some of the resemblances which can be detected.\*

\* We are indebted to Professor Collie for notes on this point.

RELATIONS BETWEEN  
ISOQUINOLINE AND  
PHENANTHRENE ALKALOIDS.



Hydrastine



In the table on p. 269, some of the formulæ are collected together. In the first place, an examination of the structures of narceine, laudanosine and papaverine will show the step-by-step change from the open-chain grouping of the amino-chain in narceine to the closed and unsaturated pyridine ring in papaverine; and it will also reveal the identical distribution of the hydroxyl radicles in the three molecules, although the outward resemblance is masked to some extent by the substitution of a methylene ether radicle in narceine for the dimethoxyl grouping common to the others.

Comparison of narceine and hydrastine brings out the alliance between the two substances; for the carbonyl and carboxyl groups in the former compound become converted into the lactonic ring of hydrastine, at the same time as the open chain is contracted into the piperidine ring.

The main skeletons of laudanosine, glaucine and apomorphine, are obviously identical, and the change from the one formula to another is accomplished by a preliminary closing of a ring between two benzene nuclei, followed by a second ring-formation by elimination of water between two hydroxyl groups.

The inter-relations between papaverine, berberine, and *isocryptopine* chloride can be seen by inspection of the formulæ on page 269.

It has not been thought necessary to do more than give these examples, for the resemblances between other analogously constituted alkaloids can easily be detected when attention has been drawn to the matter.

## G.—THE PHENANTHRIDINE GROUP

### 1. *Introductory*

The alkaloids of this group have been isolated from some species of the daffodil family (*Amaryllidaceae*) of plants. The compounds which have, up to the present, received most attention are lycorine and tazettine. These two substances are closely related. They both yield phenanthridine on degradation and can be oxidized to hydrastic acid.

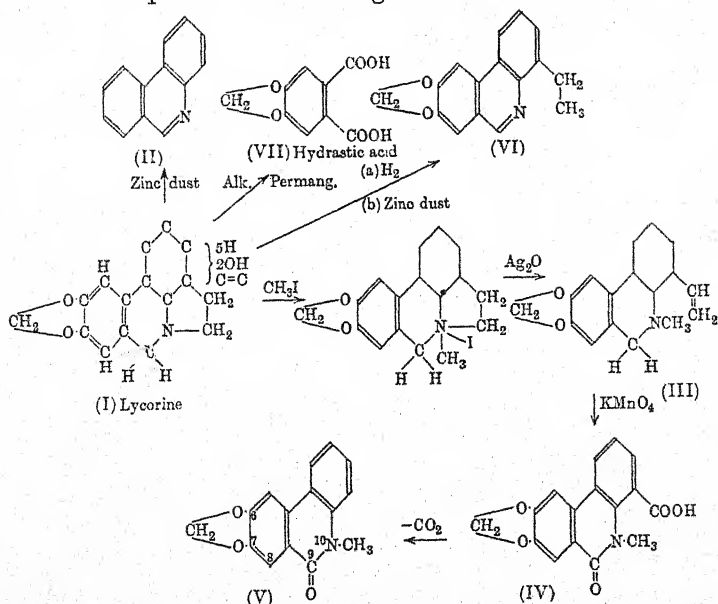
### 2. *Lycorine*

This compound has the molecular formula,  $C_{16}H_{17}O_4N$ . It is a very stable substance, but can be catalytically reduced to dihydrolycorine. The nitrogen atom is present in the tertiary



form. The action of hydriodic acid showed the absence of methoxy groups. Two of the oxygen atoms of the molecule are accounted for, as a methylenedioxy phenanthridine has been obtained from lycorine. The remaining two oxygen atoms probably exist as hydroxyl groups, but have not yet been located in the molecule. When lycorine (I.) was distilled with zinc dust it yielded some phenanthridine (II.).<sup>1</sup> A less violent method of degradation gave interesting results. Lycorine was converted into its anhydromethine (III.) by "exhaustive" methylation using methyl iodide and moist silver oxide. The anhydromethine was then oxidized with potassium permanganate to an acid,  $C_{16}H_{11}O_5N$  (IV.), which on decarboxylation yielded 6:7-methylenedioxy-10-methylphenanthridone (V.).

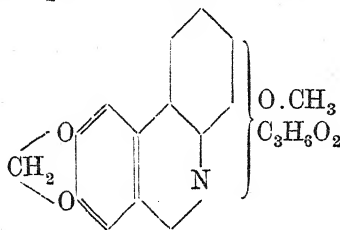
When the anhydromethine was first reduced to its dihydro-derivative and then distilled with zinc dust it yielded 6:7-methylenedioxy-1-ethylphenanthridine (VI.). The action of alkaline potassium permanganate on lycorine produced 4:5-methylenedioxy-*o*-phthalic acid (hydrastic acid) (VII.). The foregoing changes permit us to write down the carbon-nitrogen skeleton of lycorine and place in position two of the four oxygen atoms. The partial formulæ are given below.



<sup>1</sup> Kondo and Uyeo, *Ber.*, 1935, 68, [B], 1756; 1937, 70, [B], 1087.

## 3. Tazettine

Tazettine,  $C_{18}H_{21}O_5N$ , yields phenanthridine on zinc dust distillation and breaks down into hydrastic acid on oxidation. Like lycorine it may be converted into a methine base, from which 6-phenylpiperonyl alcohol was obtained by "exhaustive" methylation.<sup>1</sup> The partial structure may be written as



## H.—THE QUINAZOLINE GROUP

## 1. Vasicine (Peganine)

(a) *Introductory*.—Vasicine occurring in the leaves of the Indian plant *Adhatoda vasica* and in the seeds of *Peganum harmala*, is an interesting compound as it is the only alkaloid known with certainty to contain the quinazoline skeleton. The dried leaves of *Adhatoda vasica* in the form of cigarettes are used in the treatment of asthma, and the liquid extract as an expectorant. Vasicine may be extracted from the leaves of *Adhatoda vasica* by means of alcohol or by a mixture of ammonia and chloroform.

(b) *The Constitution of Vasicine*.—Vasicine has the molecular formula,  $C_{11}H_{12}ON_2$ . The Zerewitinoff reaction showed the presence of hydroxyl in the molecule.\*<sup>2</sup> This was confirmed by the conversion of vasicine into deoxychlorovasicine,  $C_{11}H_{11}N_2Cl$ , by the action of phosphorus oxychloride.<sup>3</sup> When the alkaloid was fused with potassium hydroxide the products identified were anthranilic and acetic acids. On oxidation with potassium permanganate vasicine yielded 4-quinazalone (I.), and on oxidation with permanganate followed by treatment with diazomethane the product was methyl-4-keto-3:4-dihydroquinazolyl-3-acetate (II.). When deoxychlorovasicine was reduced it gave deoxyvasicine,  $C_{11}H_{12}N_2$  (VII.). The deoxyvasicine molecule contains the eleven carbon and two nitrogen atoms of the

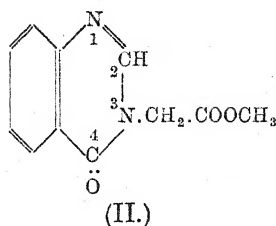
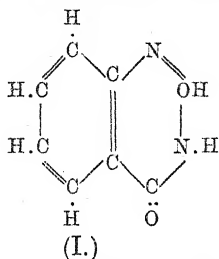
<sup>1</sup> Späth and Kahovec, *Ber.*, 1934, 67, [B], 1501.

\* See p. 197.

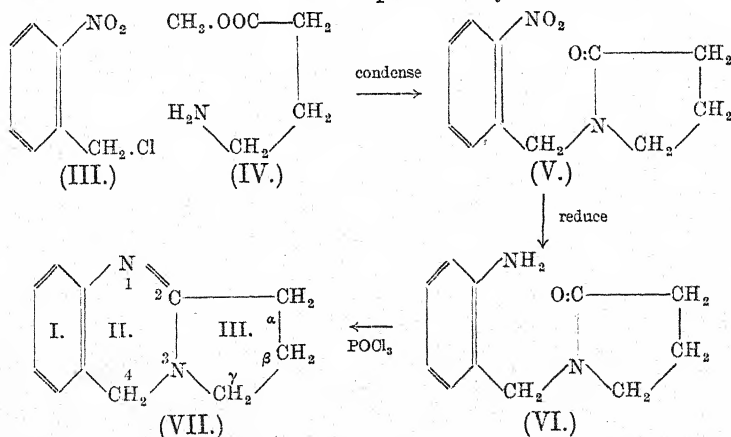
<sup>2</sup> Späth and Nikawitz, *Ber.*, 1934, 67, [B], 45.

<sup>3</sup> Ghose, *J. Ind. Chem. Soc.*, 1927, 4, 1.

parent alkaloid, and presumably the molecular skeleton of vasicine has persisted through the changes to the deoxy-derivative. A knowledge of the structure of deoxyvasicine considered along with the other results of degradation will, therefore, go a long way towards elucidating the constitution of vasicine.

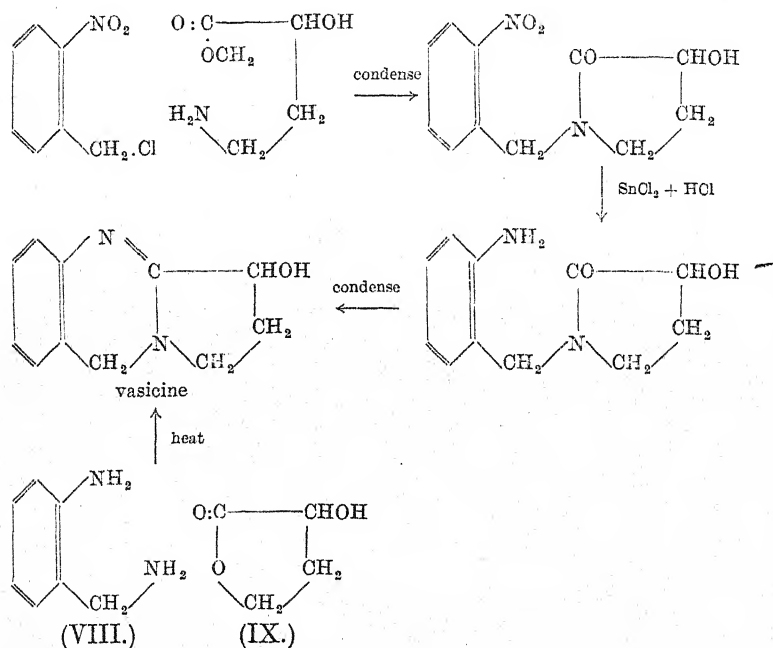


It is evident that the remainder of the problem hinges on the arrangement of the carbon atoms attached to the quinazoline skeleton. The production of the quinazolylacetic acid derivative (II.) shows nitrogen atom number 3 to be one point of linkage, and the complete skeleton of the vasicine molecule was established by the synthesis of deoxyvasicine in the following way. *o*-Nitrobenzylchloride (III.) was condensed with methyl  $\gamma$ -aminobutyrate (IV.) to yield *o*-nitrobenzylpyrrolidone (V.). This was reduced by stannous chloride to the amino-compound (VI.), which was transformed by phosphorus oxychloride into deoxyvasicine (VII.) identical with the compound obtained from natural vasicine.<sup>1</sup> The steps in the synthesis are—



<sup>1</sup> Späth, Kuffner, and Platzner, *Ber.*, 1935, 68, [B], 497; 1936, 69, [B], 255; Hanford and Adams, *J. Amer. Chem. Soc.*, 1935, 57, 921, 951.

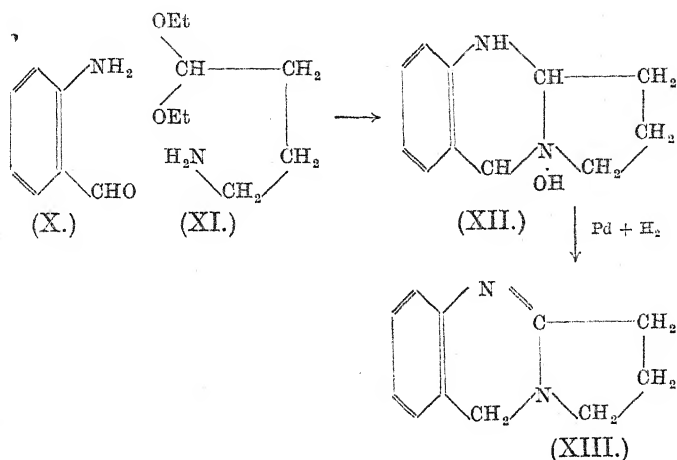
The hydroxyl group has now to be placed in the ring system to complete the structure of vasicine. There are four possible positions for this group, namely,  $\alpha$ ,  $\beta$ ,  $\gamma$  and 4 (see structure VII.). The synthesis of vasicine by two different methods leaves no doubt that the compound has its hydroxyl group attached at the  $\alpha$  position in ring III. One of the synthesis follows similar lines to those adopted for the preparation of deoxyvasicine, the other is from *o*-aminobenzylamine (VIII.) and  $\alpha$ -hydroxybutyrolactone (IX.). The steps in the two syntheses are as follows:—



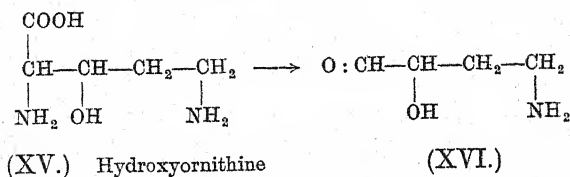
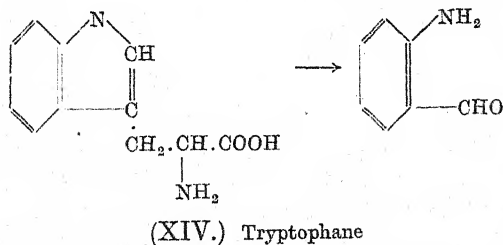
Interesting attempts have been made to synthesize vasicine and other quinazoline derivatives under "physiological" conditions.<sup>2</sup> For example, *o*-aminobenzaldehyde (X.) and the acetal of  $\gamma$ -aminobutyraldehyde (XI.) were kept together in a citrate buffer solution of pH 4.8–5.0 at 30° C. for four days and gave a good yield of 4-hydroxy-2 : 3-cyclopentanotetrahydroquinazoline (XII.), which could be reduced to deoxyvasicine (XIII.).

<sup>1</sup> Späth, Kuffner, and Platzer, *Ber.*, 1935, 68, [B], 699.

<sup>2</sup> Schöpf and Oechler, *Annalen*, 1936, 523, 1.



It is thought that in the plant the production of vasicine results from the condensation of o-aminobenzaldehyde and gamma-amino-alpha-hydroxybutyraldehyde (XVI.) and that the precursors of these may be tryptophan (XIV.) and hydroxyornithine (XV.) respectively.



## CHAPTER IX

### RECENT WORK ON THE INDOLE GROUP OF ALKALOIDS

#### A. THE ALKALOIDS OF ERGOT

##### 1. *Introductory*

THE fungus *Claviceps purpurea* develops on certain cereal crops, particularly in the seeds of rye. The sclerotium of this fungus is known as ergot, and occurs in the form of violet-black brittle grains. Ergot has long been used in medicine to stimulate muscle and particularly to excite uterine contractions. As the composition of ergot is not fully known it has to be carefully standardized for medical use. When absorbed in excess the ergot alkaloids are poisonous, and the regular use of ergotized rye bread gives rise to the human diseases known as gangrenous and convulsive ergotism. Recent work has resulted in a great increase in our knowledge of the chemical nature of the ergot alkaloids which, so far as identified, fall into two well-defined groups. On the one hand there are the laevorotatory compounds of marked physiological action, and on the other hand the substances which are dextrorotatory and physiologically weak in their effects. The relationship between the two groups is a close one. The five known laevorotatory compounds of Group I are isomeric with the five dextrorotatory compounds of Group II, and the isomerides are interconvertible.<sup>1</sup> In addition to the five pairs of isomerides there is  $\psi$ -ergotinine, which is isomeric with ergotoxine and ergotinine, and is convertible into either of these compounds.<sup>2</sup> Table I. shows the relationships and the molecular formulæ of the compounds.

It is possible that the dextrorotatory alkaloids are mostly secondary products formed during the extraction of the substances from ergot. In addition to the marked differences in optical rotation and physiological action between the two groups of alkaloids, the laevorotatory compounds possess strong residual

<sup>1</sup> Barger and Carr, *J.*, 1907, 91, 337; Kraft, *Arch. Pharm.*, 1906, 244, 336; Stoll, *Schweiz. Apoth.-Ztg.*, 1922, 60, 341.

<sup>2</sup> Smith and Timmis, *J.*, 1931, 1888.

valency, which manifests itself in a tendency to form molecular compounds.

TABLE I  
ERGOT ALKALOIDS

Molecular Formula	Group I Laevorotatory	Group II Dextrorotatory	
$C_{19}H_{23}O_2N_3$	Ergometrine	→ Ergometrinine ←	
$C_{20}H_{27}O_5N_5$	Ergosine	→ Ergosinine ←	
$C_{33}H_{35}O_5N_5$	Ergotamine	→ Ergotaminine ←	
$C_{35}H_{39}O_5N_5$	Ergotoxine	→ Ergotinine ←	↔ $\psi$ Ergotinine
$C_{35}H_{39}O_5N_5$	Ergocristine	→ Ergocristinine ←	

## 2. Decomposition Products of the Ergot Alkaloids

Four pairs of the isomerides have been subjected to careful examination and the outstanding result has been the isolation of the compound lysergic acid and its amide from each alkaloid by hydrolysis. The acid itself is obtained by using aqueous alkali, and the amide, when alcoholic alkali is the degrading agent.<sup>1</sup> It is noteworthy that the other products of decomposition from any one alkaloid are either the same in part or closely related to the products from the other alkaloids. Reference to Table II. given below shows these relationships.

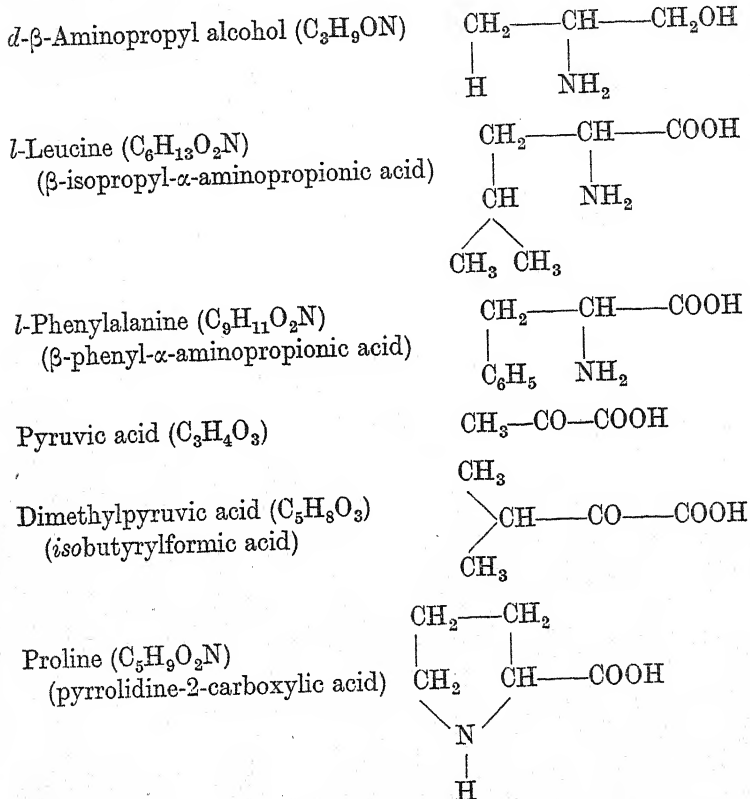
TABLE II

Alkaloids	Ergometrine Ergometrinine	Ergosine Ergosinine	Ergotamine Ergotaminine	Ergotoxine Ergotinine
Decomposition Products	Lysergic acid <i>d</i> - $\beta$ -Aminopropyl alcohol	Lysergic acid <i>l</i> -Leucine  Pyruvic acid  <i>d</i> -Proline Ammonia	Lysergic acid <i>l</i> -Phenyl- alanine Pyruvic acid  <i>d</i> -Proline Ammonia	Lysergic acid <i>l</i> -Phenyl- alanine Dimethyl- pyruvic acid <i>d</i> -Proline Ammonia

<sup>1</sup> Smith and Timmis, *J.*, 1932, 763; Jacobs and Craig, *J. Biol. Chem.*, 1934, 104, 547; 1935, 111, 455.



The structures of *d*- $\beta$ -aminopropyl alcohol, *l*-leucine, *l*-phenylalanine, pyruvic acid, dimethylpyruvic acid and *d*-proline are given below for reference.



### 3. The Structure of Lysergic Acid

Although finality has not yet been reached on the question of the structure of lysergic acid, the major problems have been solved and a substantially correct picture of the molecule may be presented.

Lysergic acid is obtained by hydrolysis of the alkaloids and has the molecular formula  $C_{16}H_{16}O_2N_2$ .<sup>1</sup> It has been isolated

<sup>1</sup> Jacobs, *J. Biol. Chem.*, 1932, 97, 739; Jacobs and Craig, *ibid.*, 1934, 104, 547; *ibid.*, 1934, 106, 393.

in two optically active isomeric forms, and when it is heated in aqueous solution it is converted into a new isomer, *isolysergic acid*. By the action of alkali on this isomer *lysergic acid* is re-formed. From measurements of their optical rotations and from a synthesis of *d*-ergometrinine from *d-isolysergic acid* it is concluded that *lysergic acid* is derived from the laevorotatory alkaloids and *isolysergic acid* from the dextro-compounds. *Lysergic acid* behaves both as an acid and a base. It contains a N-methyl group and a carboxyl group, and gives indole colour reactions. When *lysergic acid* is reduced by means of amyl alcohol and sodium it yields dihydrolysergic acid, pointing to the presence of one reducible ethylenic linkage in the molecule.

Oxidation of *lysergic acid* by nitric acid leads to a tribasic acid,  $C_{14}H_9O_8N$ . This substance may be formulated as a N-methylquinolinebetaine tricarboxylic acid (II.), as it yields quinoline (III.) on fusion with soda-lime.<sup>1</sup> When dihydrolysergic acid (IV.) is fused with potassium hydroxide 1-methyl-5-aminonaphthalene (V.) and 3:4-dimethylindole (VI.) are formed.<sup>2</sup> Taking these facts into consideration the structure (I.) given on p. 280 has been suggested for *lysergic acid*.

Rings C and D of structure (I.) would give rise to the quinoline compounds (II.) and (III.). Rings A and C would account for 1-methyl-5-aminonaphthalene (V.), the formation of which also gives a clue to the position of the indole nitrogen atom. Rings A and B would yield 3:4-dimethylindole (VI.).

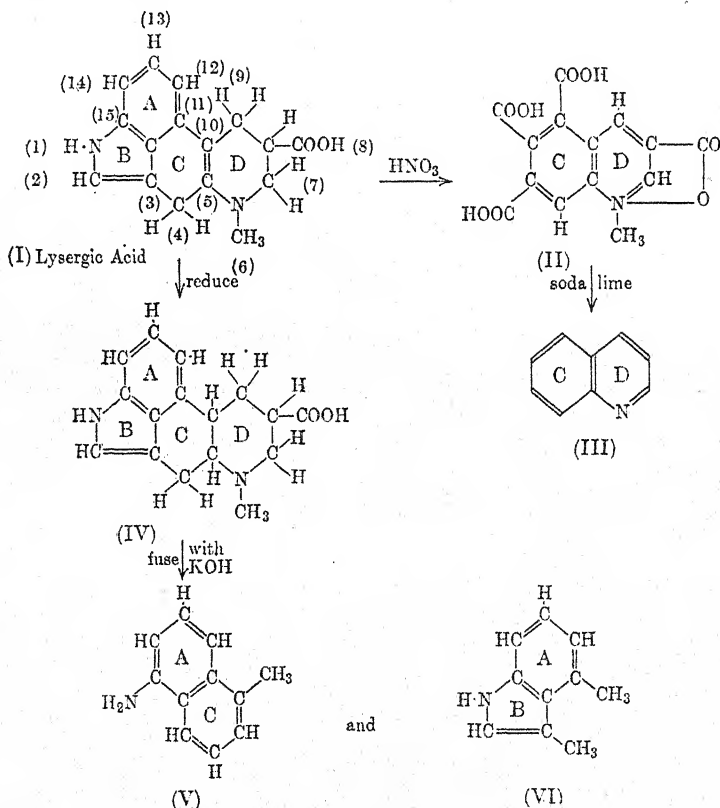
Comparison of the ultraviolet absorption spectra of *lysergic acid* and the parent alkaloids with the spectra of the corresponding reduced compounds indicates that the ethylenic linkage is conjugated with the benzene or pyrrole ring of the indole nucleus.<sup>3</sup> From these results the double carbon bond is either at position 4-5, 5-10 or 9-10. Measurements of the strengths of the basic groups in *lysergic* and *isolysergic acids* showed the former to be the weaker base. This difference in basicity is attributed to the position of the ethylenic linkage relative to the basic group, :N.CH<sub>3</sub>, in each compound. In *lysergic acid* the point of unsaturation and the basic group are nearer to one another than in *isolysergic acid*. The conversion of *lysergic acid* into *isolysergic*

<sup>1</sup> Jacobs and Craig, *Science*, 1936, 83, 38.

<sup>2</sup> Jacobs and Craig, *J. Biol. Chem.*, 1939, 128, 715.

<sup>3</sup> Jacobs, Craig, and Rothen, *Science*, 1936, 83, 166.

acid is considered to be due to the migration of the ethylenic linkage to an adjacent position. Inspection of the structure given to lysergic acid (I.) shows that of the possible positions for the ethylenic linkage, 5-10 must be selected if *isolysergic acid* is to have its unsaturated linkage further removed from the basic group and at the same time adjacent to the position occupied by the bond in lysergic acid. *Isolysergic acid*, consequently, will have the ethylenic linkage at position 9-10.<sup>1</sup>



Methylamine is produced in almost quantitative yield along with indole derivatives by the decomposition of dehydrolysergic acid. It is, therefore, reasonable to conclude that the methylamine does not come from the indole part of the molecule, but

<sup>1</sup> Craig, Shedlovsky, Gould, and Jacobs, *J. Biol. Chem.*, 1938, 125, 289.

from the hydroquinoline portion. The methyl group is consequently<sup>1</sup> shown in the structure (I.) attached to the nitrogen atom numbered 6.

To provide an asymmetric carbon atom in the lysergic acid molecule the carboxyl group must occupy position 4, 7, 8 or 9. Position 4 may be rejected as substituted indole acetic acids are unstable when heated. Dihydrolysergic acid is so stable that it can be sublimed at 300° C. Position 9 may also be rejected since migration of the double bond between positions 5-10 and 9-10 should cause ready racemization. No racemization has been detected due to the interconversions of lysergic and *iso*-lysergic acids.

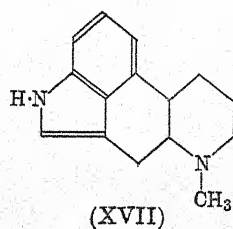
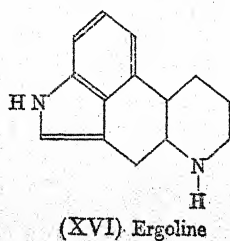
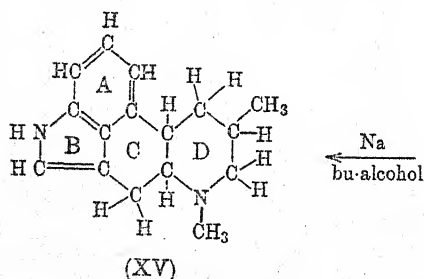
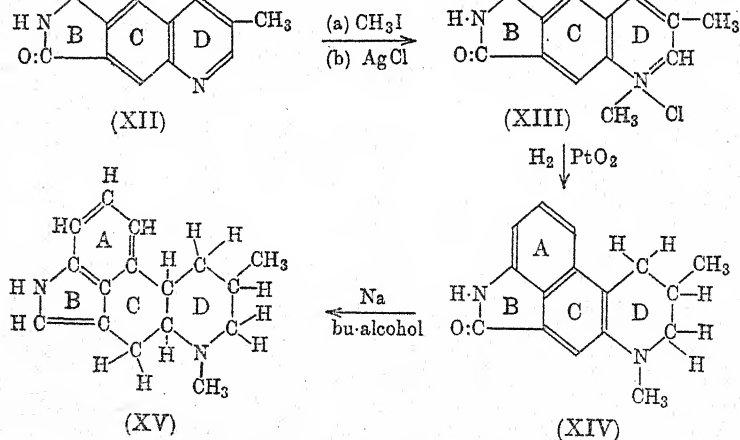
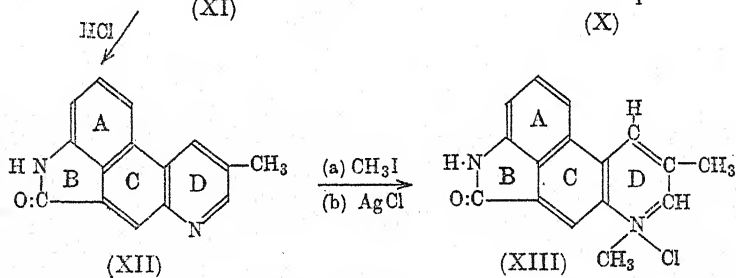
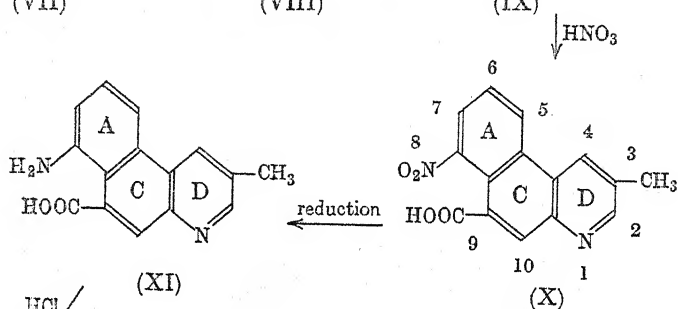
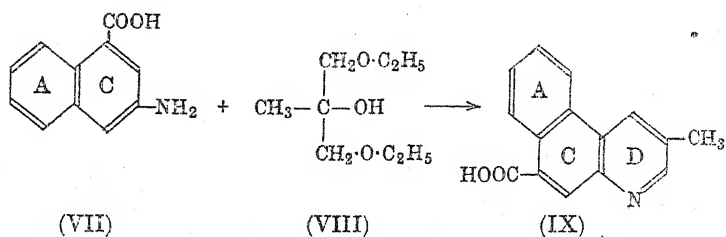
Comparison of the relative magnitudes of the basic dissociation constants of dihydrolysergic acid (IV.) and 6-methylergoline (XVII.) points to the acid having its carboxyl and basic groups in the 1:3 positions relative to one another. Position 8 is, therefore, assigned to the carboxyl group of lysergic acid.<sup>2</sup>

#### 4. The Ergolines

Turning now to the synthetic compounds related to lysergic acid, three important substances have been prepared. The parent compound has been named ergoline (XVI.), the other two are 6-methyl-ergoline (XVII.) and 6:8-dimethylergoline (XV.). The same general methods were employed in all three syntheses. The preparation of 6:8-dimethylergoline will be described as it has also been obtained from lysergic acid from natural sources. 3-Amino-1-naphthoic acid (VII.) was converted into 3-methyl-5:6-benzquinoline-7-carboxylic acid (IX.) by a modification of Skraup's synthesis in which  $\beta$ -methylglycerol  $\alpha$ -diethyl ether (VIII.) was used instead of glycerol. The benzquinoline derivative was nitrated and gave as the main product the 3-methyl-8-nitro-9-carboxylic acid derivative (X.) of the benzquinoline. Reduction of the nitro group by means of ferrous sulphate and alkali yielded the corresponding amino compound (XI.), which on treatment with hydrochloric acid was converted into the lactam (XII.). The methochloride (XIII.) of the lactam on hydrogenation using platinum dioxide

<sup>1</sup> Jacobs and Craig, *ibid.*, 1935, 111, 455.

<sup>2</sup> Craig, Shedlovsky, Gould and Jacobs, *J. Biol. Chem.*, 1938, 125, 289.



as the catalyst yielded the partially reduced compound,  $C_{16}H_{16}ON_2$  (XIV.). This derivative was further reduced by means of sodium and butyl alcohol with the formation of 6:8-dimethylergoline (XV.). This substance, which contains three asymmetric carbon atoms in the molecule, is presumably a racemic compound. Its properties are practically identical with those of the optically active base obtained from natural sources.<sup>1</sup> The resolution of the synthetic 6:8-dimethylergoline into its optically active forms and a comparison of these with the compounds from natural lysergic acid will put the matter beyond doubt. The formulæ given on p. 282 will make the steps in the synthesis clearer.

#### 5. The Structures of Ergometrine and Ergometrinine

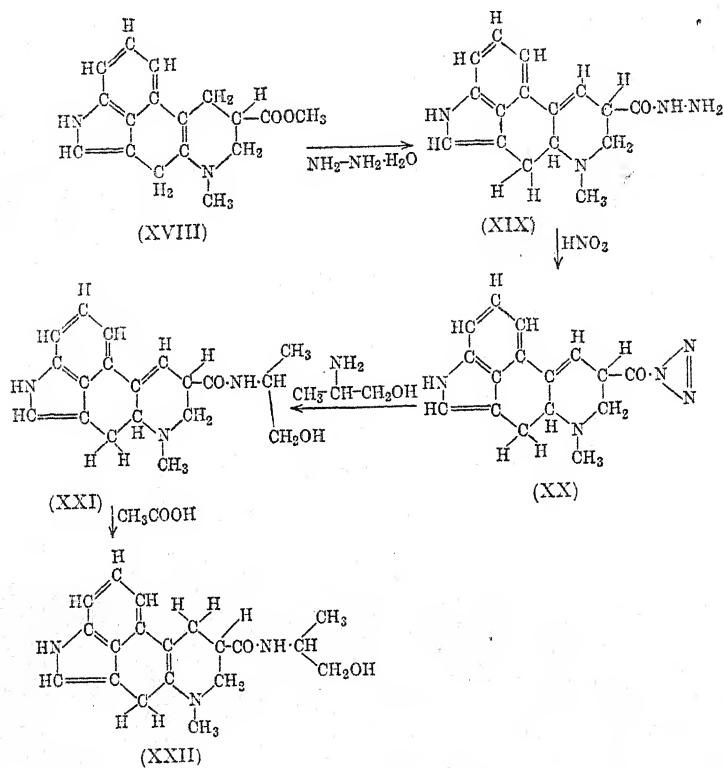
Assuming that the structure given for lysergic acid is substantially correct there remains the problem of the way in which the different parts of the alkaloid molecules are joined together.

Both ergometrine and ergometrinine on hydrolysis yield lysergic acid and *d*- $\beta$ -aminopropyl alcohol.<sup>2</sup> From this it is inferred that they are amides. Lysergic acid itself is very sensitive to acids and attempts to build up the amide from the acid and alcohol were unsuccessful. The synthesis was accomplished in the following way. Methyl lysergate (XVIII.) was treated with hydrazine and converted into *isolyserghydrazide* (XIX.). From this compound by the action of nitrous acid the corresponding azide (XX.) was isolated. The action of *d*- $\beta$ -amino-*n*-propyl alcohol on the azide gave a mixture of amides from which *d*-*isolyserg-d*- $\beta$ -hydroxyisopropylamide (XXI.) was isolated chromatographically by aluminium oxide. This amide proved to be identical with ergometrinine and like natural ergometrinine could be isomerized to ergometrine (*d*-lyserg-*d*- $\beta$ -hydroxyisopropylamide) (XXII.) by the action of acetic acid or phosphoric acid in alcohol.<sup>3</sup> The structures are as shown on p. 284.

<sup>1</sup> Jacobs and Gould, *J. Biol. Chem.*, 1937, 120, 141; 1938, 126, 67.

<sup>2</sup> Smith and Timmis, *J.*, 1937, 396; Jacobs and Craig, *Science*, 1935, 82, 16.

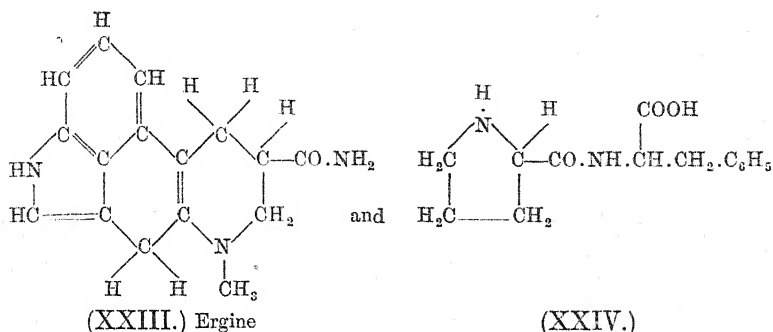
<sup>3</sup> Stoll and Hoffmann, *Z. physiol. Chem.*, 1937, 250, 7.



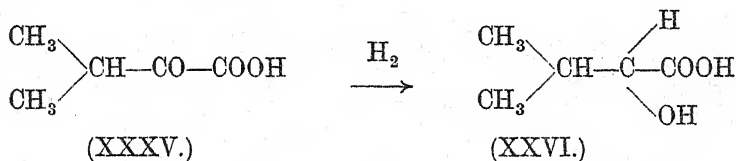
#### 6. The Structures of Ergosine, Ergotamine, Ergotoxine and their Isomers

Five products have been isolated from each of these more complex alkaloids (see Table II., p. 277). These pieces have to be fitted together in agreement with the available evidence to give the complete alkaloid molecule. The amide of lysergic acid (ergine) (XXIII.) is obtained from the alkaloids by hydrolysis with alcoholic alkali. In a similar way a peptide,  $\text{C}_{14}\text{H}_{18}\text{O}_3\text{N}_2$ , (XXIV.), was produced from ergotinine, which on further hydrolysis by strong acid yielded proline and phenylalanine. These facts point to the presence of two acid amide linkages in the alkaloidal structure. The two amides are—

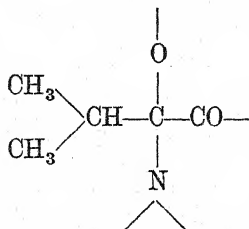




It now remains to fit these and dimethylpyruvic acid together correctly to obtain the ergotoxine-ergotinine molecules. A further step forward in the problem was taken when it was found that ergotinine after prolonged catalytic hydrogenation still yielded dimethylpyruvic acid on hydrolysis by alkali. Under the conditions of hydrogenation employed, dimethylpyruvic acid (XXV.) itself was readily reduced to  $\alpha$ -hydroxyisovaleric acid (XXVI.)

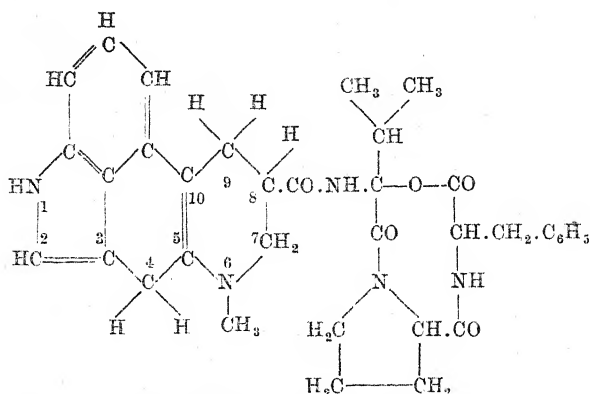


The conclusion to be drawn from these results is that the "dimethylpyruvic acid" part of the alkaloid molecule is present in a form incapable of reduction. A free keto-acid grouping may, therefore, be ruled out. The most satisfactory explanation is that the structure yielding dimethylpyruvic acid on hydrolysis is—



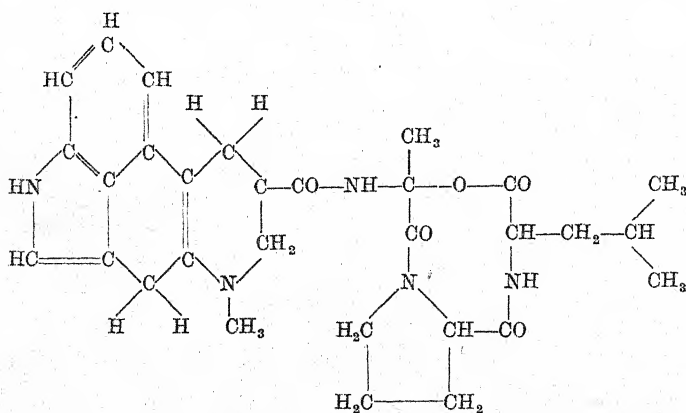
If this grouping formed  $\alpha$ -hydroxyvaline on hydrolysis of the alkaloid it would decompose readily into dimethylpyruvic acid

and ammonia. Taking all the known facts into consideration a provisional structure may now be formulated for ergotoxine (XXVII.).



(XXVII.) Ergotoxine

The isomer ergotinine will have the same arrangement of atoms but with the ethylenic linkage between carbon atoms 9 and 10. Ergotamine and ergotaminine will have the corresponding structures, but with the pyruvic acid residue in place of the dimethylpyruvic acid grouping. Similarly the ergosine (XXVIII.) and ergosinine molecules may be built up with the leucine grouping in place of the phenylalanine residue.<sup>1</sup>



(XXVIII.) Ergosine

<sup>1</sup> Jacobs and Craig, *J. Biol. Chem.*, 1938, 122, 419.

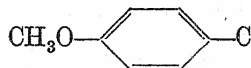
## B.—THE HARMALINE ALKALOIDS

The seeds of the plant *Peganum harmala* contain three alkaloids of the indole group.

Harmaline <sup>1</sup>	. . . . .	$C_{13}H_{14}ON_2$
Harmine <sup>2</sup>	. . . . .	$C_{13}H_{12}ON_2$
Harmalol <sup>3</sup>	. . . . .	$C_{12}H_{12}ON_2$

From a comparison of the formulæ, it appears likely that harmaline is dihydroharmine.<sup>4</sup> This proves to be the case; for both compounds yield the same tetrahydroharmine on reduction, and harmaline is converted into harmine by gentle oxidation. When boiled with hydrochloric acid, both harmine and harmaline are demethylated, showing that each of them contains a methoxy-group. The products of these reactions<sup>5</sup> are respectively harmol,  $C_{12}H_{10}ON_2$ , and harmalol,  $C_{12}H_{12}ON_2$ . Harmine is a secondary base; for with methyl iodide it yields first methylharmine and then methylharmine methiodide.

On oxidation with strong nitric acid,<sup>6</sup> harmaline gives harminic acid,  $C_8H_6N_2(COOH)_2$ , and *m*-nitroanisic acid. The production of this last substance shows that the harmine molecule must contain the grouping :



Oxidation of harminic acid with dilute nitric acid<sup>7</sup> produced some *isonicotinic* acid; so that the harmine structure must have in it the nucleus



<sup>1</sup> Goebel, *Annalen*, 1841, 38, 363.

<sup>2</sup> Fritzsche, *Annalen*, 1847, 64, 365.

<sup>3</sup> O. Fischer, *Ber.*, 1897, 28, 2481; 1905, 38, 329; *Prince Luitpold Festschrift*, Erlangen, 1901 (see *Chem. Soc. Abstracts*, 1905, i. 229).

<sup>4</sup> O. Fischer, *Ber.*, 1897, 28, 2481.

<sup>5</sup> O. Fischer and Tauber, *Ber.*, 1897, 30, 2482.

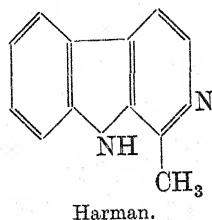
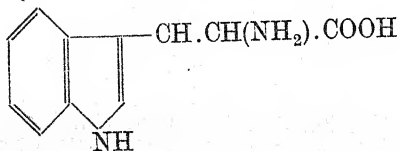
<sup>6</sup> O. Fischer and Boesler, *Ber.*, 1912, 45, 1934.

<sup>7</sup> O. Fischer and others, *Ber.*, 1914, 47, 99.

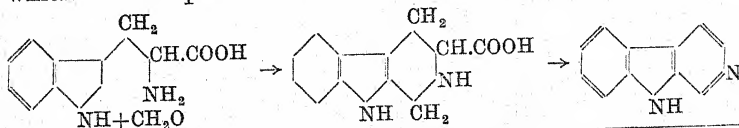
Further, Perkin and Robinson <sup>1</sup> found that harmine condenses with benzaldehyde to yield a benzyldene-harmine; which suggests by analogy that harmine contains a methyl group in the  $\alpha$ -position to a nitrogen atom, like  $\alpha$ -picoline. Finally, by the elimination of the methoxy-group from harmine, O. Fischer <sup>2</sup> obtained a compound harman,  $C_{12}H_{10}N$ , which proved to be the key to the problem.

Perkin and Robinson in 1912 suggested that harmine contained a fused system of benzene, pyrrol, and pyridine rings. The results of oxidation, given above, indicate that the pyrrol ring is in the centre, since derivatives of both the other rings appear among the disintegration products.

Now in 1903, Hopkins and Cole <sup>3</sup> obtained a base by oxidizing tryptophane with ferric chloride; and this base was identified by Perkin and Robinson <sup>4</sup> with O. Fischer's harman.



It will be noticed that this conversion of tryptophane into harman demands an extra pair of carbon atoms, which are probably derived from decomposition products of another tryptophane molecule. Their exact provenance is not of major importance, however. The main point is that the indole nucleus of tryptophane can give rise to harman; so that the presence of the same indole kernel in harman is made probable.<sup>5</sup> Tryptophane can be condensed with formaldehyde to yield *norharman*, which seems to place the matter beyond doubt.



<sup>1</sup> Perkin and Robinson, *J.*, 1912, 101, 1778.

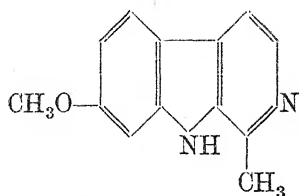
<sup>2</sup> O. Fischer, *Luitpold Festschrift*, 1901.

<sup>3</sup> Hopkins and Cole, *J. Physiol.*, 1903, 29, 451.

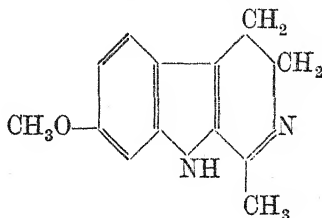
<sup>4</sup> Perkin and Robinson, *J.*, 1919, 115, 933, 971.

<sup>5</sup> See also Kermack, Perkin, and Robinson, *J.*, 1921, 119, 1602; 1922, 121, 1872.

Fitting together the above evidence, Perkin and Robinson arrived at the following formulæ for harmine and harmaline:



Harmine.



Harmaline.

## C.—THE YOHIMBE ALKALOIDS

### 1. Introductory

The source of these alkaloids is Yohimbe, the bark of the tree *Pausinystalia yohimba* Pierre ex Beille (Fam. Rubiaceae), indigenous to the French Congo and the Cameroons. The chief alkaloidal constituent of the bark is yohimbine. Some of the other yohimbe alkaloids are isomeric with yohimbine, and  $\gamma$ -yohimbine, mesoyohimbine and yohimbene, on degradation yield the same derivative, yohimbol, obtained from yohimbine.<sup>1</sup> The structure of yohimbine will be dealt with here.

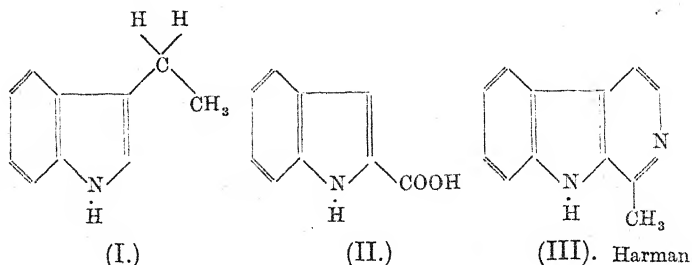
### 2. Yohimbine

Yohimbine (XIX.) has the molecular formula  $C_{21}H_{26}O_3N_2$ . Two of the oxygen atoms of the molecule are present in a methyl ester grouping, as on hydrolysis with potassium hydroxide solution, yohimbine yields yohimbic acid,  $C_{20}H_{24}O_3N_2$  (XX.), which can be esterified with methyl alcohol to re-form yohimbine. The remaining oxygen atom is present in a secondary alcoholic group.<sup>2</sup> When yohimbic acid is decarboxylated the alcohol yohimbol,  $C_{19}H_{24}ON_2$  (XXI.) results. A valuable clue to the structure of yohimbine was obtained when 3-ethylindole (I.) and indole-2-carboxylic acid (II.) were identified as products of alkali fusion of yohimbic acid, and the problem was taken a stage further when harman (III.) was isolated from the products of the distillation of the acid.<sup>3</sup>

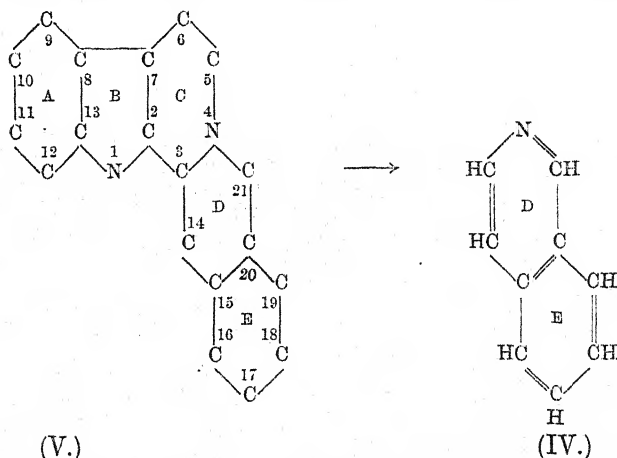
<sup>1</sup> Fourneau and Fiore, *Ber.*, 1930, 63, 1638, 2961.

<sup>2</sup> Barger and Field, *J.*, 1915, 107, 1025; Field, *ibid.*, 1923, 123, 3004; *Ber.*, 1927, 60, 1009.

<sup>3</sup> Warnat, *Ber.*, 1927, 60, 1118; Barger and Scholz, *J.*, 1933, 614; *Helv. Chim. Acta*, 1933, 16, 1343.

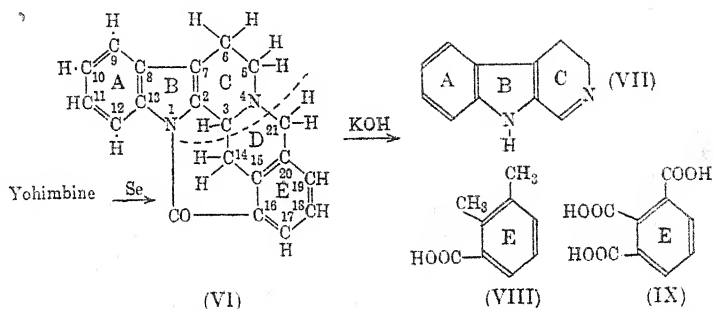


The environment of both nitrogen atoms is thus known and twelve of the carbon atoms are accounted for. On zinc distillation yohimbine yielded some *isoquinoline* (IV.).<sup>1</sup> The production of these compounds is explained by formulating the yohimbine skeleton (V.) as a system of five condensed rings.



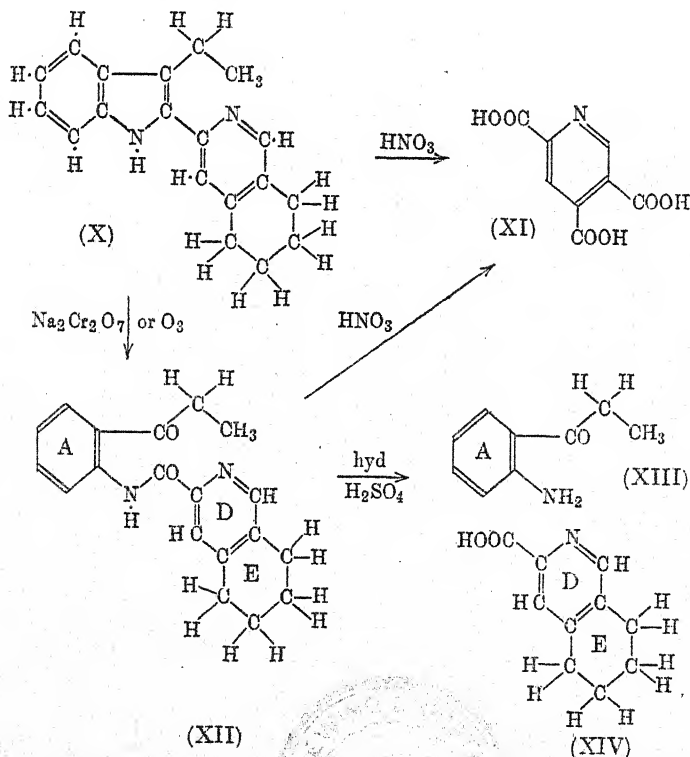
This structural arrangement is supported by evidence from other directions. When yohimbine is dehydrogenated with selenium three compounds are formed, ketoyobyrine,  $C_{20}H_{16}ON_2$  (VI.), tetrahydroyobyrine,  $C_{19}H_{20}N_2$  (X.) and yobyrine,  $C_{19}H_{16}N_2$  (XV.). Ketoyobyrine, which contains the twenty carbon atoms of yohimbic acid, when heated with potassium hydroxide in amyl alcohol, breaks down into *norharman* (VII.), 2:3-dimethylbenzoic acid (VIII.) and hemimellitic acid (IX.). These changes may be formulated in the following way, the ketoyobyrine molecule splitting at ring D.

<sup>1</sup> Winterstein and Walter, *Helv. Chim. Acta*, 129, 170, 577.



The production of 2:3-dimethylbenzoic acid and hemimellitic acid has an additional importance as their formation points to the ester grouping of yohimbine being located at carbon atom 16 of ring E.

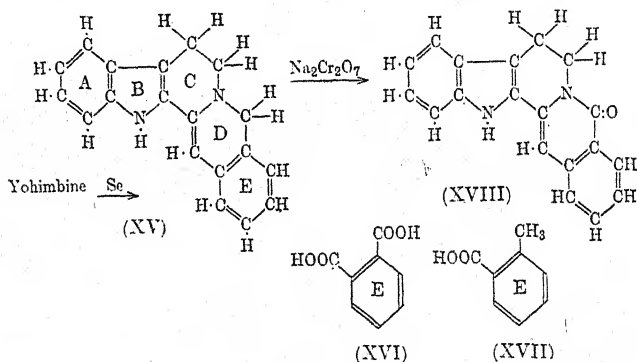
Tetrahydroxybyrine (X.) on oxidation with nitric acid breaks





down to yield berberonic acid (pyridine-2:4:5-tricarboxylic acid) (XI.). When the oxidation is effected by ozone or chromic acid a compound,  $C_{19}H_{20}O_2N_2$  (XII.), is produced, which also yields berberonic acid by the action of nitric acid, and on hydrolysis yields *o*-aminopropiophenone (XIII.) and 5:6:7:8-tetrahydroisoquinoline-3-carboxylic acid (XIV.). Tetrahydroyobyrine is, consequently, given the structure shown, as this readily accounts for the formation of the products obtained.<sup>1</sup>

Similarly, the decomposition products of yobyrine (XV.) fit into the same structural scheme.<sup>2</sup> When yobyrine is oxidized by means of sodium dichromate in acetic acid it furnishes *o*-phthalic acid (XVI.), *o*-toluic acid (XVII.), and oxoyobyrine,  $C_{19}H_{14}ON_2$  (XVIII.). These changes are represented as follows:



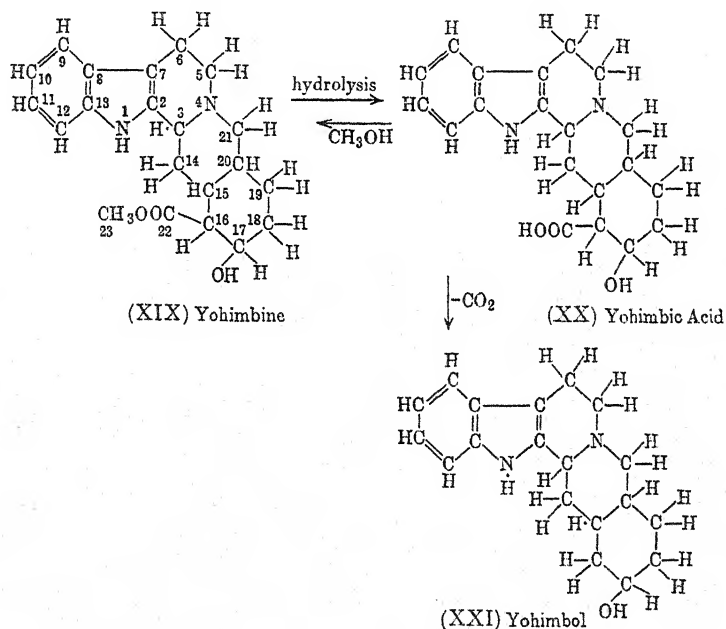
Turning now to the positions occupied by the ester and hydroxyl groups in the yohimbine molecule, the ester grouping is attached to carbon atom 16 in ring E (see structures V. and VI.), as 2:3-dimethylbenzoic acid (VIII.) has been obtained from yohimbic acid, and *m*-toluic acid has been isolated from the decomposition products of both yohimbine and yohimbic acid.

The position of the alcoholic hydroxyl group is less certain. Reference to the structure given for yohimbine (XIX.) shows

<sup>1</sup> Scholz, *Helv. Chim. Acta*, 1935, 18, 923.

<sup>2</sup> Mendlik and Wibaut, *Rec. trav. chim.*, 1929, 48, 191; 1932, 50, 91; Barger and Scholz, *J.*, 1933, 614.

that there are two available positions in ring D and three in ring E. The positions in ring D may be excluded from further consideration as the appearance of harman (III.) as a decomposition product entails carbon atom 14 being in an unoxidized condition in order to yield a methyl group. Carbon atom 21 may also be ruled out as it goes to form a methyl group in both dimethylbenzoic and *m*-toluic acids.<sup>1</sup> This leaves places 17, 18 and 19 of ring E as possible positions for the group.<sup>2</sup> No decision has yet been reached on this problem. The structure of yohimbine may be written down as follows, with the hydroxyl group shown provisionally at carbon atom 17.



### 3. Synthetic Compounds related to Yohimbine

Although yohimbine itself has not yet been synthesized several closely related substances have been prepared. The same general methods were employed in these syntheses, and in

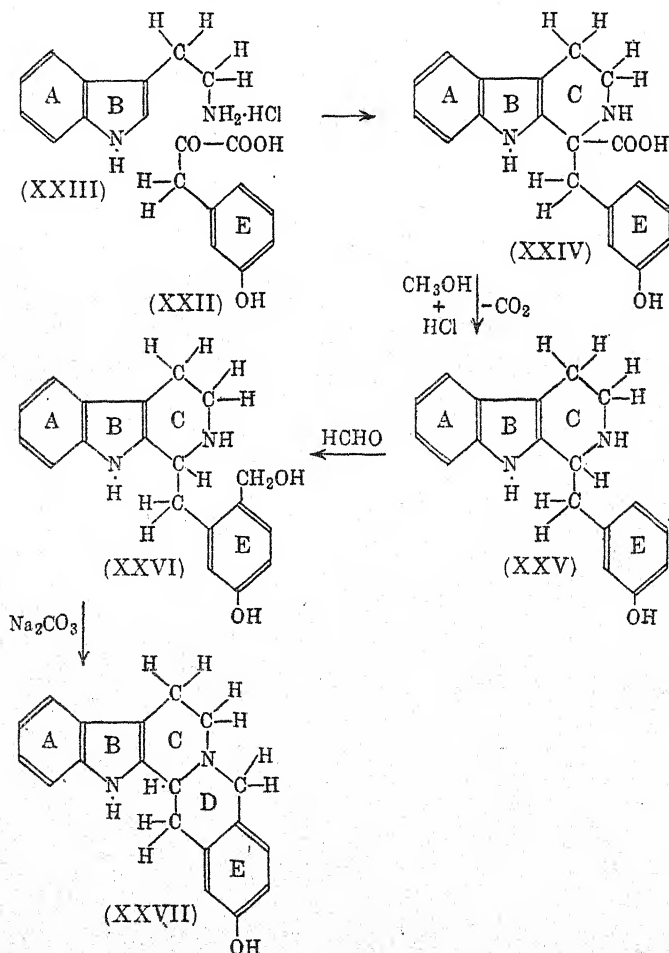
<sup>1</sup> Hahn and Werner, *Annalen*, 1935, 520, 107.

<sup>2</sup> Hahn, Kappes, and Ludewig, *Ber.*, 1934, 67, 686.

consequence the preparation of one compound will suffice to demonstrate the scheme of reactions.

#### 4. The Synthesis of Hexadehydroyohimbol

When *m*-hydroxyphenylpyruvic acid (XXII.) was allowed to stand in contact with the hydrochloride of tryptamine (3- $\beta$ -aminoethylindole) (XXIII.) in slightly acid solution for some days at 25° C., condensation took place with the formation of



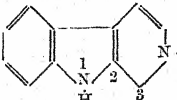
3-*m*-hydroxybenzyl-3:4:5:6-tetrahydronorharman-3-carboxylic acid (XXIV).<sup>\*</sup> This compound was decarboxylated by means of methyl alcoholic hydrogen chloride to 3-*m*-hydroxybenzyl-3:4:5:6-tetrahydronorharman (XXV.). The action of warm formaldehyde solution on this last-named substance led to the formation of 3-(3-hydroxy-6-hydroxymethylbenzyl)-3:4:5:6-tetrahydronorharman (XXVI.). When the hot aqueous solution of the hydrochloride of this compound was made alkaline with sodium carbonate, ring-closure was effected and a hexadehydro-yohimbol (XXVII.) isolated.<sup>2</sup> 17-Methoxy-18-hydroxy and 17:18-dimethoxy derivatives have also been prepared.<sup>3</sup>

#### D.—STRYCHNINE AND BRUCINE

##### 1. Introductory

These are the two most important alkaloids occurring in the seeds and wood of various *Strychnos* plants. Strychnine was isolated from *Strychnos Nux-vomica* in 1817 and brucine a few years later. The two compounds are closely related, yielding the same acid on oxidation with chromic acid, and it is now established beyond doubt that brucine is a dimethoxystrychnine. The molecular structure of strychnine is a compact of fused rings and the difficulties encountered in probing this formation were very great. Investigations have been carried on for over a century and step by step the constitution has been elucidated. Finality has not yet been reached, but the principal features of the molecular structure have been established and several provisional structures (I.), (II.) and (III.) have been put forward (see p. 296).

It will be noticed that these three structures are similar except for an uncertainty regarding the point of attachment of the carbon atom numbered 16.

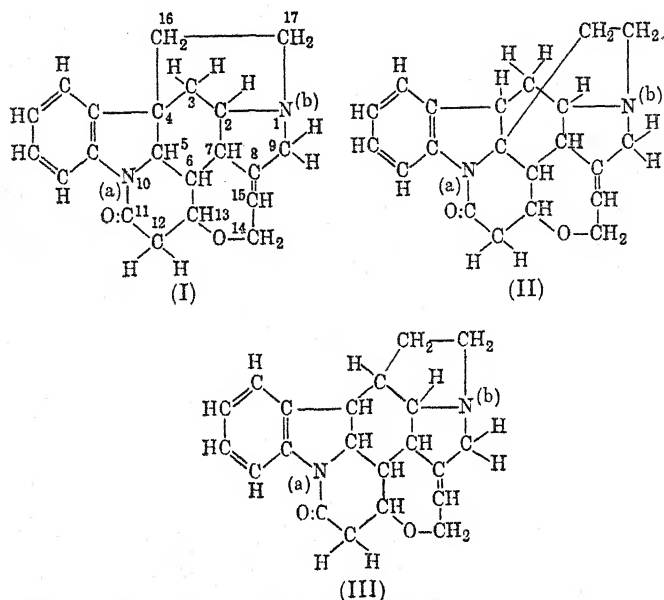
\* The norharman ring system,  is also known as the

4-carboline system. It has been proposed, however, to alter this to  $\beta$ - or 3-carboline to bring the numbering of the system into harmony with that of other condensed nuclear types.<sup>1</sup>

<sup>1</sup> Gulland, Robinson, Scott, and Thornley, *J.*, 1929, 2924.

<sup>2</sup> Hahn and Werner, *Annalen*, 1935, 520, 123.

<sup>3</sup> Hahn and Hansel, *Ber.*, 1935, 71, [B], 2192.



Suggested formulae for strychnine

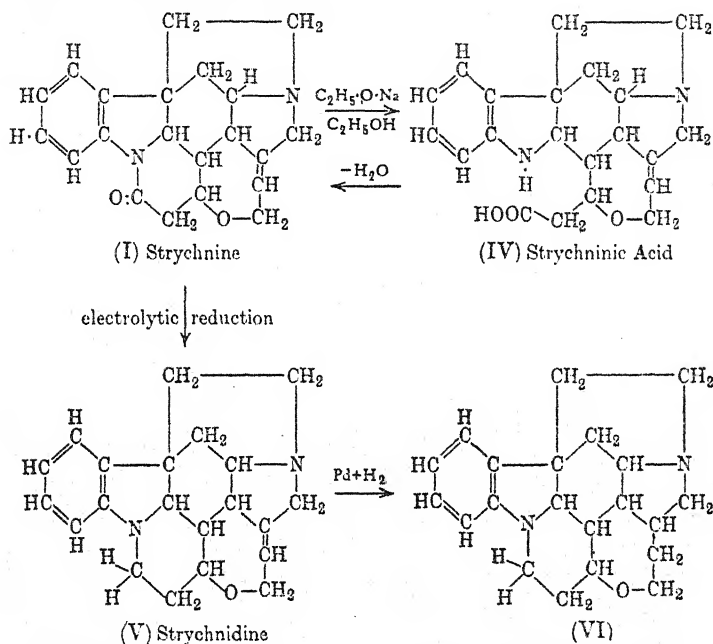
## 2. The Constitutions of Strychnine and Brucine

The strychnine molecule,  $C_{21}H_{22}O_2N_2$  (I.) contains one neutral and one basic tertiary nitrogen atom, yielding salts of the types  $B.HCl$  and  $B_2.H_2SO_4$ .<sup>1</sup> On hydrolysis with alcoholic sodium ethoxide strychnine was converted into strychninic acid,  $C_{21}H_{24}O_3N_2$  (IV.), from which strychnine was readily reformed by dehydration. The two new groups produced in the formation of strychninic acid are a carboxyl and a secondary amine, as the compound forms metallic salts and yields a nitrosamine,  $C_{20}H_{22}ON(N:NO).COOH$ , when treated with nitrous acid.<sup>2</sup> These results suggest that the structure in strychnine giving rise to  $>N-H$  and  $-COOH$  in strychninic acid, without the loss of a carbon or nitrogen atom, is a cyclic amide. The presence of the amide grouping in strychnine is confirmed by the results of electrolytic reduction. Here the reduction proceeds normally and strychnidine,  $C_{21}H_{24}ON_2$  (V.) is produced owing to the con-

<sup>1</sup> Regnault, *Annalen*, 1838, 26, 17.

<sup>2</sup> Loebisch and Schoop, *Monats.*, 1886, 7, 83; Tafel, *Annalen*, 1891, 264, 50; Gal and Étard, *Bull. Soc. chim.*, 1879, [ii.], 31, 98.

version of the acid amide group,  $\text{>N-CO-}$ , into an amine,  $\text{>N-CH}_2\text{-}$ . In strychnidine both nitrogen atoms are basic in properties.<sup>1</sup> Using structure (I.) of strychnine for purposes of illustration strychninic acid (IV.) and strychnidine (V.) will have the following structures:—



Strychnidine like strychnine contains one ethylene linkage as it can be catalytically reduced to dihydrostrychnidine (VI.). The second oxygen atom of strychnine is chemically inert and as strychnine can be reduced to an oxygen-free base without loss of carbon the oxygen atom must be present in a cyclic ether formation.<sup>2</sup> The nature of the two oxygen and two nitrogen atoms of strychnine is now understood. Strychnine condenses readily with benzaldehyde in alkaline alcoholic solution to yield benzylidenestrychnine (VII.). This reaction requires the presence of an activated methylene group, and in this case the activation must be ascribed to an adjacent carbonyl group.

<sup>1</sup> Tafel, *Annalen*, 1892, 268, 229; 1898, 301, 285; Skita and Frank, *Ber.*, 1911, 44, 2862; Clemo, Perkin, and Robinson, *J.*, 1927, 1589, 2389.

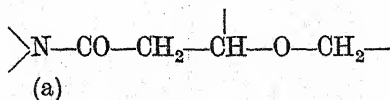
<sup>2</sup> Tafel, *Ann. Chem.*, 1898, 301, 285; Perkin and Robinson, *J.*, 1929, 964.

The structure  $\text{>N}^{\text{10}}\text{—CO}^{\text{11}}\text{—CH}_2^{\text{12}}\text{—}$  is, therefore, present in the strychnine molecule. The chain of atoms has been further extended. When strychnine was oxidized with potassium permanganate a ketonic acid, strychninonic acid,  $\text{C}_{21}\text{H}_{20}\text{O}_6\text{N}_2$  (VIII.), was formed.<sup>1</sup> This could be reduced with sodium amalgam to strychninolic acid,  $\text{C}_{21}\text{H}_{22}\text{O}_6\text{N}_2$  (IX.). On examination this latter acid turned out to be a secondary alcoholic monocarboxylic acid without any basic properties, and it was concluded that both nitrogen atoms were amidic in character.

When strychninolic acid was allowed to stand for some hours in sodium hydroxide solution it split off glycollic acid (X.), and was converted into strychninolone,  $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_2$  (XI.). These mild reaction conditions were unlikely to affect the two amide groups, and it was concluded that the carboxyl group of glycollic acid was the free acidic group of strychninolic acid. The production of glycollic acid is best explained by assuming the

presence of the grouping  $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—O—CH}_2\text{—COOH}$  in strychninolic acid (IX.), and consequently of an ether oxygen in strychnine.<sup>2</sup> This oxygen atom in strychnine is presumably in the neighbourhood of the acid amide grouping, as a comparison of some of the properties of strychnine and strychnidine showed that the ether oxygen in strychnine entered into several changes which did not occur in strychnidine. Thus strychnine on reduction with phosphorus and hydrogen iodide was converted into deoxystrychnine,  $\text{C}_{21}\text{H}_{26}\text{ON}_2$ , by removal of the ether oxygen and further reduction. Treated in the same way strychnidine did not give up its ether oxygen.

Again, strychnine when heated with water or ammonia in methyl alcohol was converted into *iso*strychnine, which contains an alcoholic hydroxyl group formed from the ether oxygen by scission. Strychnidine does not undergo this type of isomerism. For these and other reasons the grouping

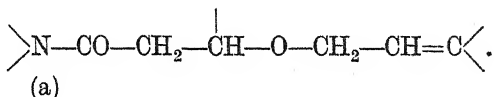


<sup>1</sup> Leuchs *et al.*, *Ber.*, 1908, 41, 1711; 1909, 42, 2494; 1910, 43, 2417; 1936, 69, 47.

<sup>2</sup> Fawcett, Perkin, and Robinson, *J.*, 1928, 3082.

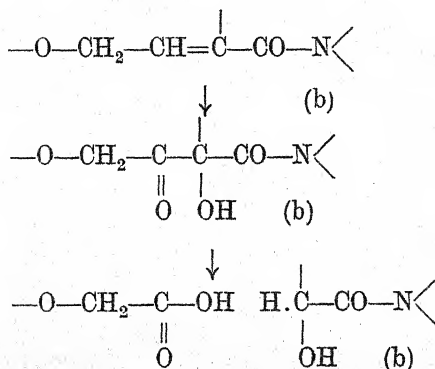


is considered to be present in the strychnine molecule. Reverting to strychninonic acid (VIII.), this substance is a ketonic monocarboxylic acid and like strychninolic acid contains two neutral nitrogen atoms, undoubtedly due to the presence of two  $\text{>N-CO-}$  groups in the molecule. The ketonic and carboxyl groups of strychninonic acid must arise from an ethylene linkage in a ring; and bearing in mind the formation of glycollic acid from strychninolic acid the ether oxygen must be placed in the structure as follows,  $\text{—O—CH}_2\text{—CH=C<}$ . Add to this chain the structure already established and we have

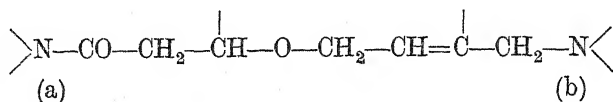


This chain of atoms can be extended to include the second nitrogen atom of strychnine.

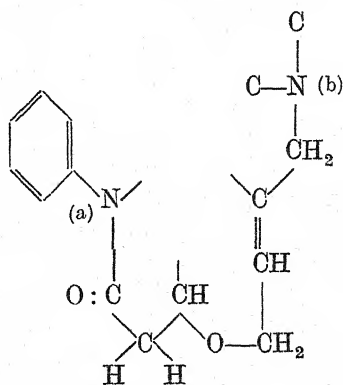
Dihydrostrychninonic acid,  $\text{C}_{21}\text{H}_{22}\text{O}_6\text{N}_2$ , (XII.), which is isomeric with strychninolic acid, was formed in small quantity during the permanganate oxidation of strychnine. The appearance of this compound can be explained if it is assumed that a carbonyl group is adjacent to the ethylene linkage and that oxidation at the double carbon bond takes the course:—



Making this addition to the atomic chain already formulated,<sup>1</sup> the sequence of atoms in strychnine is—



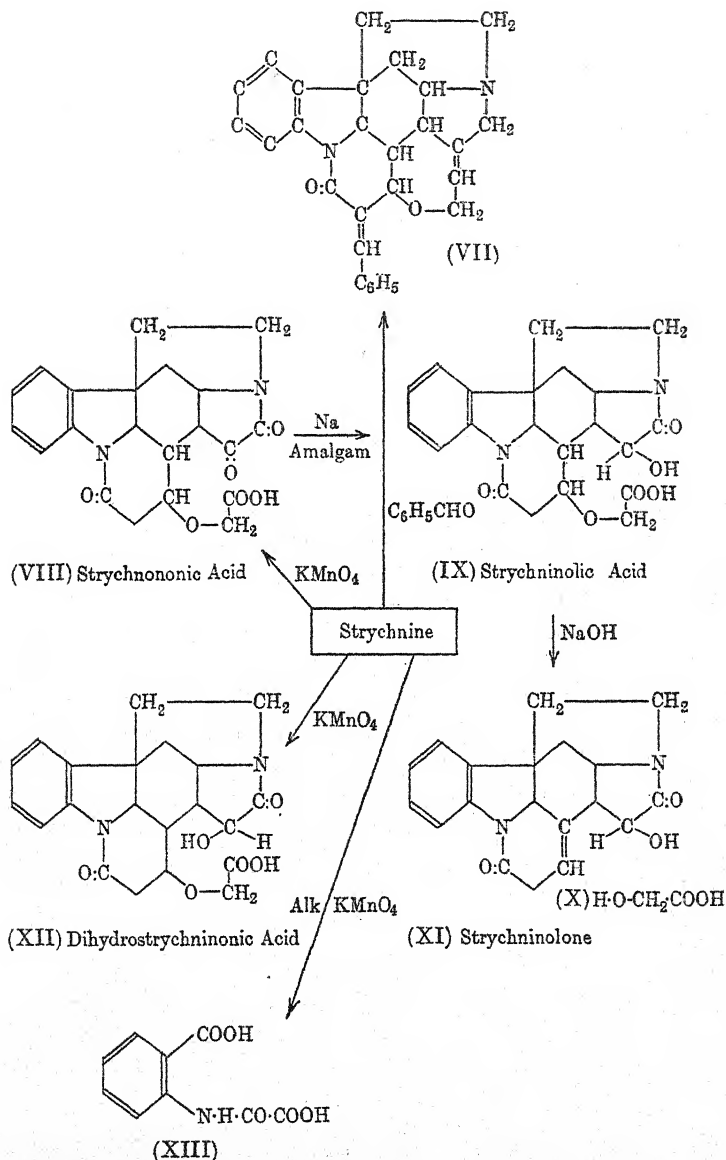
One of the characteristic properties of strychnine is the ease with which it is nitrated and sulphonated. This coupled with the fact that various benzene derivatives have been detected amongst the products of decomposition makes it certain that there is at least one benzene nucleus in the molecule. Picric acid and 3:5-dinitrobenzoic acid have been isolated from the products of oxidation with nitric acid, and N-oxalylanthranilic acid (XIII.) was obtained by alkaline permanganate oxidation of strychnine.<sup>2</sup> Comparison of the reactions of strychnine and strychnidine showed that they are related to one another as acylanilines are to alkyilanilines. This confirms the presence of a benzene nucleus attached to an acid amide group as indicated by the production of N-oxalyl-anthranilic acid. A benzene nucleus can now be added to the chain of atoms already established.



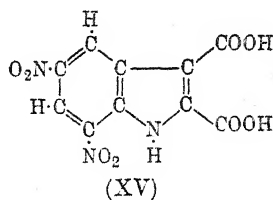
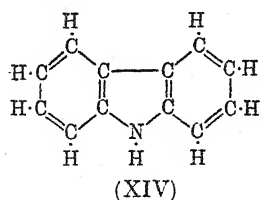
<sup>1</sup> Robinson, *Proc. Roy. Soc.*, 1931, [A], 130, 431.

<sup>2</sup> Shenstone, *J.*, 1885, 47, 139; Menon, Perkin, and Robinson, *J.*, 1930, 842; Späth and Bretschneider, *Ber.*, 1930, 63, [B], 2997.

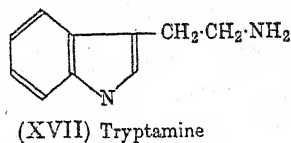
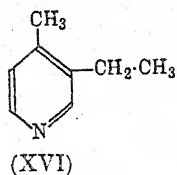
The following structures will make the chemical changes described in the foregoing paragraphs clearer.



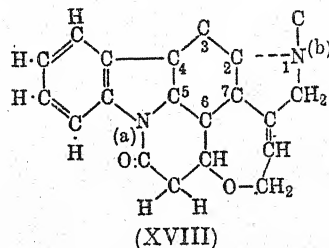
Turning now to some other products obtained from strychnine and its relatives. Methylstrychnine mixed with methylalcoholic potash and heated to 250° C. yielded some carbazole <sup>1</sup> (XIV.). When strychnine was treated with hot dilute nitric acid, nitration and oxidation proceeded in stages and finally the chief product isolated was 5:7-dinitroindole-2:3-dicarboxylic acid (XV.).<sup>2</sup>



When strychnine was broken down under as mild conditions as possible, using alcoholic potassium hydroxide, three basic compounds were isolated. Two of these have been identified, one as 4-methyl-3-ethylpyridine (XVI.) and the other as 3-β-aminoethylindole (tryptamine) (XVII.). The latter substance is of particular interest as it contains both nitrogen atoms of strychnine.<sup>3</sup>



The atomic arrangement of strychnine may now be further elaborated to (XVIII.) :—



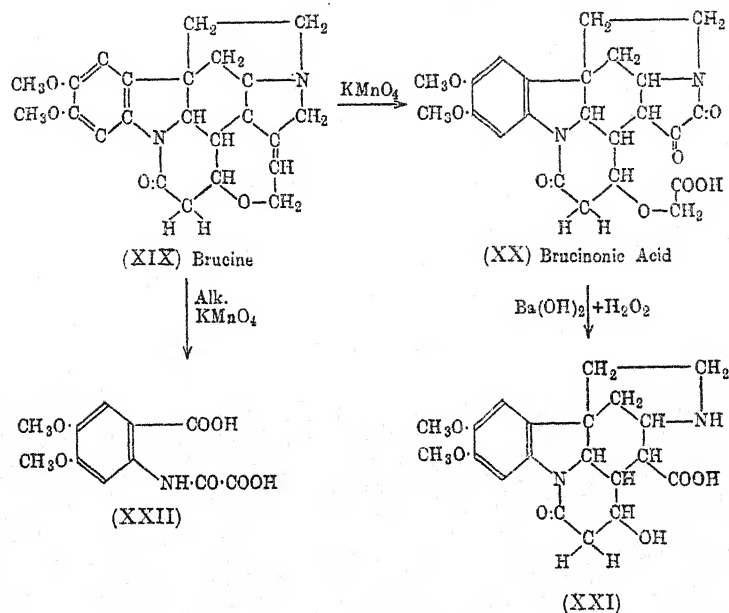
The basic tertiary nitrogen atom (b) may be put into a five-membered ring, as brucinonic acid (XX.) (which is related to

<sup>1</sup> Clemo, Perkin, and Robinson, *J.*, 1927, 1589.

<sup>2</sup> Menon and Robinson, *J.*, 1931, 773.

<sup>3</sup> Kotake, *Proc. Imp. Acad. Tokyo*, 1936, 12, 99; Clemo, *J.*, 1936, 1695.

brucine (XIX.) as strychninonic acid (VIII.) is to strychnine) by oxidation with barium peroxide was converted into an amino-acid,  $C_{20}H_{22}O_0N_2$  (XXI.), which could not be converted into the corresponding lactam.<sup>1</sup> An amino-acid derived from a six-membered ring would be expected to yield a lactam without difficulty.



Two carbon atoms and four accompanying hydrogen atoms have now to be fitted in to complete the molecular structure. There is no doubt that these are present as  $-\text{CH}_2-\text{CH}_2-$  and  $\text{CH}_3$

not as  $-\text{CH}-$ . The production of tryptamine (XVII.) indicates this, and the Kuhn-Roth micro-examination\* of various strychnine derivatives gave negative results for the presence of a methyl group attached to carbon.<sup>3</sup>

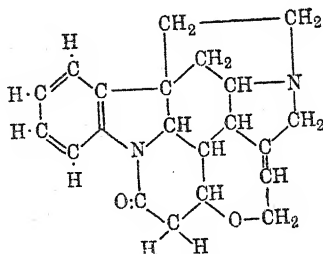
<sup>1</sup> Leuchs and Kröhnke, *Ber.*, 1932, 65, 218, 980.

\* This method involves oxidation with chromic acid under drastic conditions, distillation and estimation of the acetic acid produced.<sup>2</sup>

<sup>2</sup> Kuhn and L'Orsa, *Z. angew. Chem.*, 1931, 44, 847; Kuhn and Roth, *Ber.*, 1933, 66, [B], 1274.

<sup>3</sup> Reynolds and Robinson, *J.*, 1934, 592.

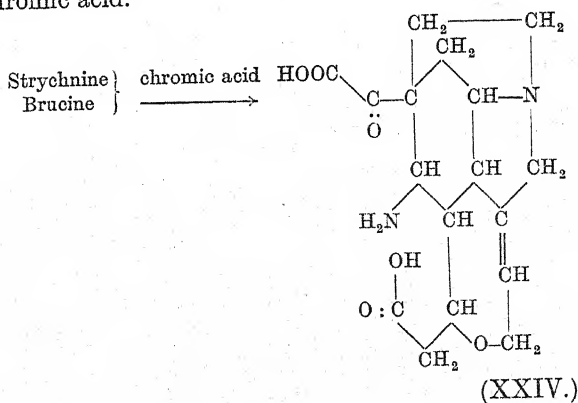
The production of tryptamine is also strong evidence in favour of the  $-\text{CH}_2-\text{CH}_2-$  grouping being attached to carbon atom 4. The structure of strychnine (XXIII.) may now be completed.



(XXIII) Strychnine

The numerous products of the degradation of strychnine and its relatives can, on the whole, be explained on the basis of this structure.

Brucine has been formulated as dimethoxystrychnine (XIX.). This is supported by the fact that on oxidation with alkaline permanganate it yields 4:5-dimethoxy-N-oxalylanthranilic acid (XXII.).<sup>1</sup> When the benzene nucleus of strychnine or brucine is destroyed, the same degradation product has, in a number of instances, been isolated. For example, both strychnine and brucine are converted into the same acid (XXIV.) on oxidation with chromic acid.<sup>2</sup>

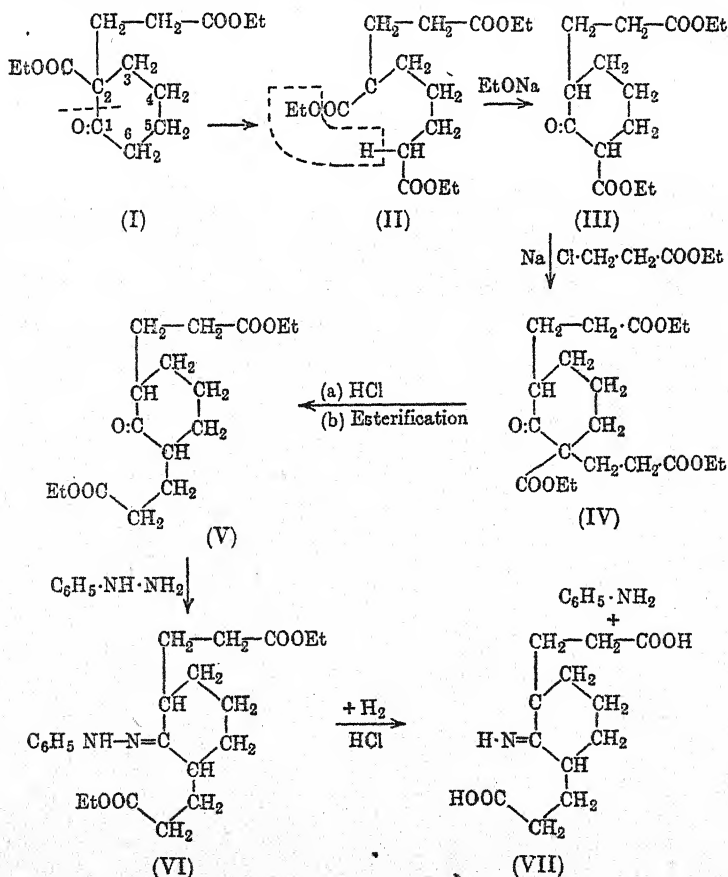


<sup>1</sup> Spath and Bretschneider, *loc. cit.*

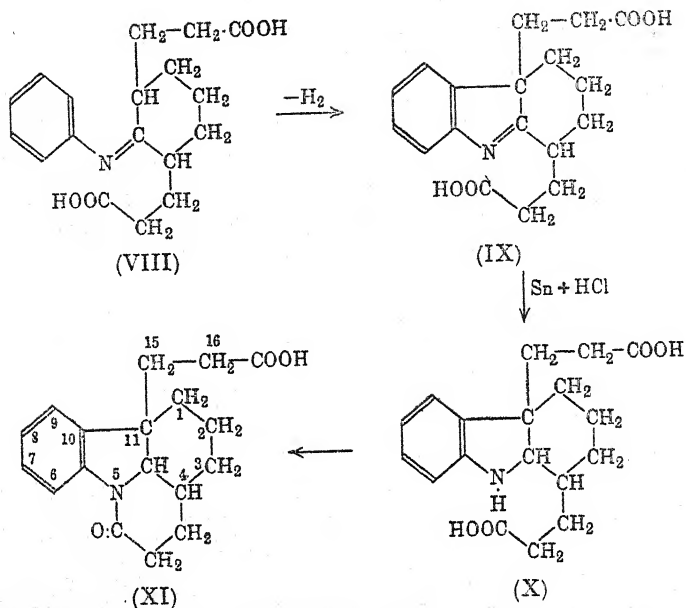
<sup>2</sup> Wieland and Münster, *Annalen*, 1929, 469, 216; 1930, 480, 39; Cortese, *Annalen*, 1929, 476, 280; Leuchs *et al.*, *Ber.*, 1929, 62, 2176, 2303; 1930, 63, 439, 1045.

3. *Synthetic Compounds related to Strychnine*

A beginning has been made on the synthesis of strychnine derivatives by the preparation of the lactam of hexahydrocarbazole-4:11- $\beta\beta'$ -dipropionic acid (XI.). This compound was synthesized in the following way. Ethyl 2-carbethoxycyclohexanone-2- $\beta$ -propionate (I.) was converted into ethyl 6-carbethoxycyclohexanone-2- $\beta$ -propionate (III.) by means of boiling alcoholic sodium ethoxide. This molecular rearrangement was evidently due to alcoholysis with the formation of the ester (II.) followed by ring-closure in a new position. The keto-ester (III.) produced was warmed with sodium in benzene and then refluxed with ethyl  $\beta$ -chloropropionate to yield ethyl 6-carbethoxycyclohexanone-2:6- $\beta\beta'$ -dipropionate (IV.). From this the







carbethoxy group was split off by heating with hydrochloric acid, and the resulting acid esterified. The ester (V.) was converted into the phenylhydrazone (VI.). The alcoholic solution of the hydrazone was treated with dry hydrogen chloride. The product was then reduced by means of tin and hydrochloric acid and the lactam of hexahydrocarbazole-1:11-ββ'-dipropionic acid (XI.) isolated.<sup>1</sup> This change of a phenylhydrazone into a carbazole derivative is a variation of the Fischer indole synthesis<sup>2</sup> and has also been applied to the production of simpler reduced carbazoles.<sup>3</sup> These transformations have been explained by assuming that the hydrazone (VI.) is reduced to aniline and the keto-imine (VII.). Elimination of ammonia from these two latter compounds would lead to the substituted imine (VIII.). Oxidative action accompanied by ring closure would lead to the carbazolenine derivative (IX.). Finally, reduction with tin and hydrochloric acid would afford the hexahydrocarbazole acid (X.), which would yield the lactam (XI.) by loss of one

<sup>1</sup> Openshaw and Robinson, *J.*, 1937, 941.

<sup>2</sup> Fischer et al., *Ber.*, 1883, 16, 2245; 1884, 17, 559; 1886, 19, 1567.

<sup>3</sup> Drechsel, *J. pr. Chem.*, 1888, 33, 69.

molecule of water. The changes described are formulated on pp. 305-6.

This is an important synthesis as the introduction of amino groups at carbon atoms 3 and 16 in place of hydrogen and carboxyl followed by ring closure by the elimination of one molecule of ammonia would lead to a compound, which it should be possible to obtain from strychnine by degradation.

## CHAPTER X

### THE ANTHOCYANINS

#### 1. *Introductory*

AN examination of plant pigments proves that they are, roughly, divisible into two classes. On the one hand are the plastid pigments which are in some way intimately associated with the organized protoplasmic structure of the plant; whilst on the other hand we have soluble pigments, existing in solution in the sap of cells. These soluble pigments are termed anthocyanins.<sup>1</sup>

In view of the number and variety of the tints exhibited by flowers, it may appear that the term anthocyanin is a very loose one covering a multitude of colouring materials whose only relation with each other lies in the fact that they occur naturally in the sap of plants; but research has shown this idea to be erroneous. It seems practically established that the separate anthocyanins contain similar nuclei, no matter how much they may differ in colour from one another; and the wide variations of tint in flowers are to be ascribed to slight alterations in constitution which leave the main anthocyanin skeleton intact. Thus the anthocyanins may be regarded as a chemical class in the same way as it is customary to speak of the proteins, the carbohydrates, or the fats.

Although 250 years have passed since Boyle<sup>2</sup> published an investigation of the colour changes which take place when extracts from flowers are treated with acids and alkalis, it is only comparatively recently that much progress has been made in the study of the anthocyanin group.<sup>3</sup> The unstable nature of the compounds and the difficulty of preparing them in a pure state

<sup>1</sup> A complete account of the history of the anthocyanins as well as of their botanical significance is to be found in Miss Wheldale's book, *The Anthocyanin Pigments of Plants* (1916). For briefer accounts, see Everest, *Science Progress*, 1915, 9, 597, and Willstätter, *Ber.*, 1915, 47, 2831.

<sup>2</sup> Robert Boyle, *Experiments and Considerations Touching Colours*, 1664.

<sup>3</sup> A bibliography of the literature is to be found in Miss Wheldale's *Anthocyanin Pigments of Plants*, or in Perkin and Everest's *Natural Organic Colouring Matters*.

militated against research in this field. It was not until 1903 that an anthocyanin was first obtained in a crystalline condition by Griffiths.<sup>1</sup>

The next important stage in the history of the subject is marked by Grafe's discovery<sup>2</sup> that certain of the anthocyanins occurred in plants in the form of glucosides.

Meanwhile, on the botanical side of the problem a considerable amount of work had been carried out, chiefly dealing with the mode of formation of the anthocyanins in plants. Miss Wheldale<sup>3</sup> first suggested that anthocyanins might be formed from glucosides in the flavone or xanthone series by the action of oxidases; she indicated<sup>4</sup> that there are a certain number of anthocyanin types which give rise to a definite series of colour varieties.<sup>5</sup>

Having now surveyed the outlines of the anthocyanins' history from the chemical standpoint, it will be convenient, in the remainder of this chapter, to abandon the chronological method and deal with the present-day work in an order which will render the subject more readily comprehensible.

## 2. *The Methods of Extracting the Pigments from Flowers*

The choice of a suitable raw material from which to extract flower pigments is the first step which must be taken; and here two alternatives present themselves, for either fresh flowers or dried petals might be selected as the best source of the required product. The anthocyanins, under certain conditions, are unstable substances; and from this point of view it might be thought best to work up fresh flowers rather than to risk the chance of decomposition taking place during the drying process. As against this, there are certain practical arguments. In the first place, plants are in flower only during a short period of the year and in certain definite localities; so that the choice of fresh flowers as a source of anthocyanins would entail the necessity of carrying out the extraction of the pigment at fixed times and

<sup>1</sup> Griffiths, *Chem. News*, 1904, 89, 249; *Ber.*, 1903, 36, 3959.

<sup>2</sup> Grafe, *Sitzber. k. Akad. Wien*, 1906, 115, I., 975; 1909, 118, I., 1033; 1911, 120, I., 765.

<sup>3</sup> Wheldale, *Proc. Phil. Soc. Camb.*, 1909, 15, 137.

<sup>4</sup> Wheldale, *Proc. Roy. Soc.*, 1909, 81, [B], 44.

<sup>5</sup> Nierenstein and Wheldale, *Ber.*, 1911, 44, 3487.

places, and would demand the simultaneous collection of a very large number of flowers if any great quantity of raw material were required. Secondly, in fresh flowers the plant enzymes are still active, and their influence might make itself disagreeably marked in the course of the extraction. The substitution of dried petals for fresh flowers obviates both these difficulties, but on the other hand there is the possibility of a loss of anthocyanin owing to decomposition during the process of drying. Balancing one set of disadvantages against the other, it is found in practice better to employ the dried material than to use fresh flowers; and the extraction is generally carried out by using finely ground dried petals.

The solvent chosen for the removal of the pigment from the petals of flowers or the skins of berries varies, of course, according to the nature of the anthocyanin present. Water alone suffices to dissolve the colouring material of the cornflower<sup>1</sup>; hydrochloric acid in methyl alcohol solution is used for the rose,<sup>2</sup> the hollyhock,<sup>3</sup> the mallow,<sup>4</sup> the peony,<sup>5</sup> and the bilberry<sup>6</sup>; dilute alcohol is employed to remove the pigments from the larkspur<sup>7</sup> and the scarlet pelargonium<sup>8</sup>; whilst acetic acid is found to be the best solvent in the cases of the grape<sup>9</sup> and whortleberry.<sup>10</sup>

After the pigment has been obtained in solution it may be purified by one of three main methods<sup>11</sup>:—

1. Precipitation and crystallization of the chloride.
2. Purification by suitable reagents and crystallization of the chloride.
3. Separation in the form of a picrate and subsequent conversion into the chloride.

Under the first head come such cases as the precipitation of the chloride from alcoholic solution by means of ether. Examples

<sup>1</sup> Willstätter and Everest, *Annalen*, 1913, 401, 189.

<sup>2</sup> Willstätter and Nolan, *Annalen*, 1915, 408, 1.

<sup>3</sup> Willstätter and Martin, *Annalen*, 1915, 408, 110.

<sup>4</sup> Willstätter and Mieg, *Annalen*, 1915, 408, 122.

<sup>5</sup> Willstätter and Nolan, *Annalen*, 1915, 408, 136.

<sup>6</sup> Willstätter and Zollinger, *Annalen*, 1915, 408, 86.

<sup>7</sup> Willstätter and Mieg, *Annalen*, 1915, 408, 61.

<sup>8</sup> Willstätter and Bolton, *Annalen*, 1915, 408, 42.

<sup>9</sup> Willstätter and Zollinger, *Annalen*, 1915, 408, 86.

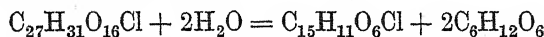
<sup>10</sup> Willstätter and Mallison, *Annalen*, 1915, 408, 15.

<sup>11</sup> *Ibid.*, 1915, 408, 160.

of the second category are to be found in the preparation of the cornflower pigment, which occurs as an alkali salt and can be purified by precipitating its aqueous solution with alcohol; and in the purification of the larkspur anthocyanin by heating it with dilute hydrochloric acid. In the picrate method the picrate is formed in the usual manner, purified, and then decomposed by a concentrated solution of hydrochloric acid in methyl alcohol.

### 3. The Constitutions of Cyanin and Cyanidin

The pigment extracted from the cornflower is termed cyanin; and it is generally prepared in the form of its chloride, which is found to have the composition  $C_{27}H_{31}O_{16}Cl$ .<sup>1</sup> When this substance is heated for a few minutes with 20 per cent. hydrochloric acid, it is hydrolysed, yielding two molecules of glucose and one molecule of a crystalline substance which has been named cyanidin chloride<sup>2</sup>:



Cyanin chloride.

Cyanidin chloride.

Glucose.

This reaction proves that cyanin is a diglucoside of the new body, cyanidin\*; and, since glucose is colourless and cyanidin is coloured, this cyanidin forms the chromophoric portion of the pigment molecule.

The general structure of cyanidin has been established by its synthesis from quercetin,<sup>3</sup> and it may be well to give the complete synthetic process here, in order to show how cyanidin can actually be prepared from purely artificial materials.

In the Kostanecki synthesis<sup>4</sup> of quercetin (see scheme on p. 312), 2-hydroxy-4:6-dimethoxy-acetophenone (I.) is condensed with dimethoxyprotocatechuic aldehyde (II.) yielding 2'-hydroxy-4':6':3:4-tetramethoxychalkone (III.). On heating this for twenty-four hours with dilute hydrochloric acid, 1:3:3':4'-tetramethoxyflavone (IV.) is produced. Treatment of this with amyl nitrite and hydrochloric acid converts

<sup>1</sup> Willstätter and Nolan, *Annalen*, 1914, 408, 1.

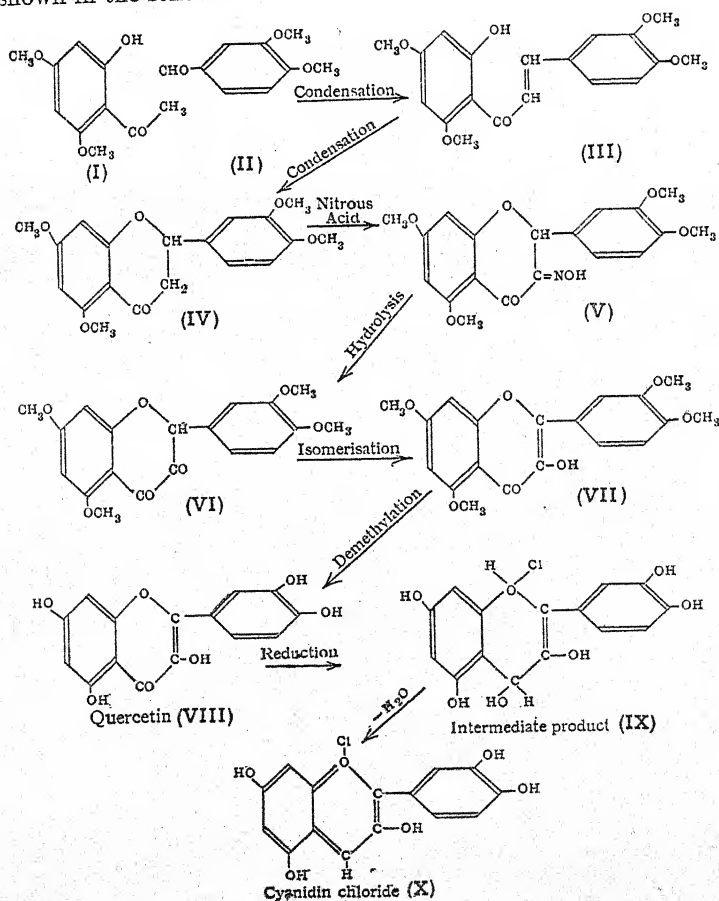
<sup>2</sup> Willstätter and Everest, *Annalen*, 1913, 401, 1.

\* From this is derived the class-name *anthocyanidins* to indicate the non-glucosidal portions of the anthocyanins.

<sup>3</sup> Willstätter and Mallison, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 769.

<sup>4</sup> Kostanecki and Tambor, *Ber.*, 1904, 37, 793; Kostanecki, Lampe, and Tambor, *ibid.*, 1402.

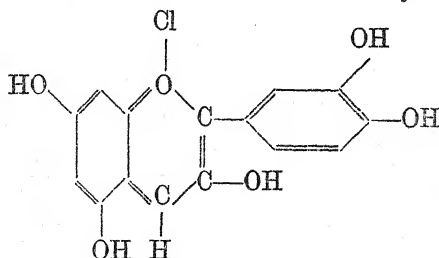
it into the corresponding *isonitroso*-compound (V.), the methylene group next the carbonyl being attacked in the usual way. Hydrolysis of the *isonitroso*-compound splits off hydroxylamine leaving a ketone (VI.); after which isomerization occurs by the production of the enolic form, resulting in the production of 1:3:3':4'-tetramethoxyflavonol (VII.), which on demethylation with hydriodic acid yields quercetin (VIII.). When quercetin is reduced with sodium amalgam or magnesium in alcoholic solution containing hydrochloric acid and mercury, cyanidin chloride is formed, though the yield is very small. Apparently the reaction involves the formation of an intermediate product (IX.), which then loses a molecule of water, as shown in the scheme.





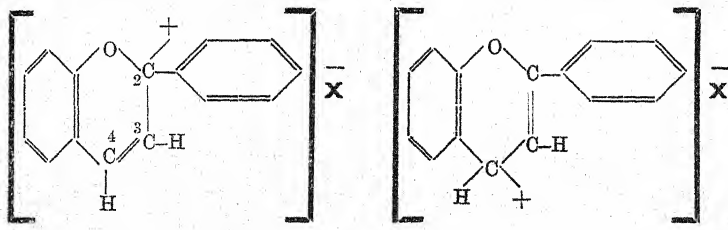
Another synthesis has been devised by Robertson and Robinson.<sup>1</sup>

An examination of the formula ascribed to cyanidin chloride



will show that it contains a peculiar heterocyclic nucleus: the pyrylium system which was discovered by Decker and Fellenberg.<sup>2</sup> The reason for assuming that this grouping is present lies in the consideration of the basic nature of the cyanidin molecule. Most of the oxonium salts, those of dimethylpyrone, for example, are susceptible to hydrolysis in aqueous solution; which points to the ordinary oxonium complex being weakly basic. Pyrylium compounds, on the other hand, are much more stable in solution than the commoner oxonium derivatives; and the behaviour of the cyanin salts in this respect tends to prove that they resemble pyrylium derivatives rather than such compounds as dimethylpyrone hydrochloride. The analysis of the cyanin salts also indicates that they are not akin to the normal oxonium hydrochloride, as they contain too little hydrogen to correspond with such a structure. On these grounds the pyrylium formula has been proposed.

On the other hand evidence has been brought forward that the anthocyanins exist as carbonium compounds and that carbon atom 2 or 4 is the seat of ionization.<sup>3</sup> The structures are:—



<sup>1</sup> Robertson and Robinson, *J.*, 1928, 1526.

<sup>2</sup> Decker and Fellenberg, *Annalen*, 1908, 364, 1.

<sup>3</sup> Dillthey *et al.*, *J. pr. Chem.*, 1931, 131, 1; 1933, 138, 42; Hill, *J.*, 1935, 85; Hill and Melhuish, *ibid.*, 1161.

To bring all the relevant evidence into agreement it has been suggested that the salts may tautomerize or resonate between these two forms.<sup>1</sup>

#### 4. *The Properties of Cyanin and Cyanidin Chlorides*

The chloride of cyanin, when prepared in the usual manner, contains two and a half molecules of water of crystallization. Under the microscope, its rhombic leaflets appear tinted between grey-violet and brownish-yellow. In dilute solutions of sulphuric acid it appears red with a tinge of violet. It is very slightly soluble in cold water, alcohol, or dilute sulphuric acid; but is easily soluble in hot water and moderately soluble in 7 per cent. acid. When sodium carbonate is added to its solution, the colour becomes first violet and then blue. Its behaviour when its aqueous solutions are diluted is peculiar. The colour of the solution weakens much more rapidly than might be anticipated and the solution may eventually become colourless. The tint of the anthocyanin can be restored either by evaporating the solution or by adding a large excess of acid. It therefore seems reasonable to suppose that the case is one of hydrolytic dissociation accompanied by intramolecular rearrangement. With ferric chloride, cyanin gives a blue tint in alcoholic solutions and a violet tinge in aqueous solutions<sup>2</sup>; whilst with lead acetate it gives a characteristic lead salt.<sup>3</sup>

Turning now to cyanidin, it is found to crystallize with one molecule of water, which is retained with extraordinary tenacity. It is a brownish-red substance giving, when dissolved in dilute acids or alcohol, a red solution with a tinge of violet. Insoluble in water, it is readily soluble in alcohols; very slightly soluble in dilute hydrochloric acid but comparatively soluble in 7 per cent. sulphuric acid. With sodium carbonate it gives the same colour change as cyanin, turning first to blue and then to violet. The hydrolytic dissociation of cyanidin is much more marked than that of its parent anthocyanin; for when hot water is added to its alcoholic solution a violet precipitate is produced. The reaction with ferric chloride is slightly different also; for in alcohol a stable blue

<sup>1</sup> Shriner and Moffett, *J. Amer. Chem. Soc.*, 1939, 61, 1474; 1940, 62, 2711; 1941, 63, 1694.

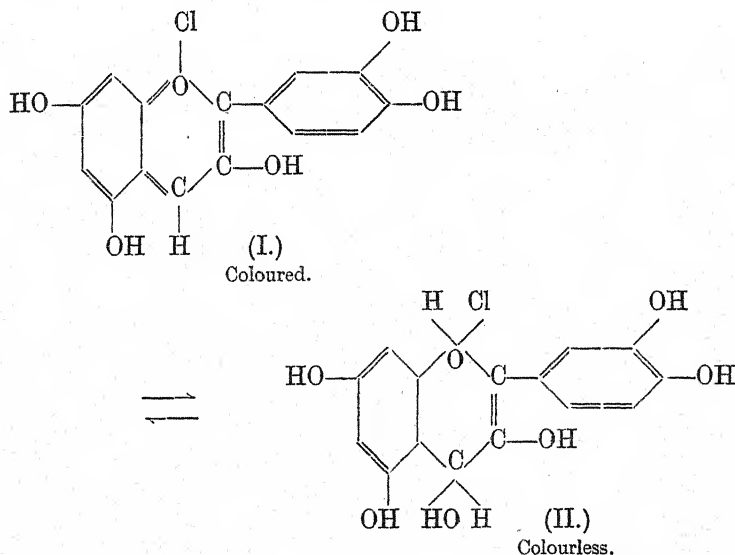
<sup>2</sup> Willstätter and Mieg, *Annalen*, 1915, 408, 124.

<sup>3</sup> Willstätter and Everest, *Annalen*, 1913, 401, 225.

coloration is produced by cyanidin; whereas in aqueous alcoholic solution only an unstable violet tint is observed.<sup>1</sup> As in the case of cyanin, lead acetate yields a characteristic salt of cyanidin.<sup>2</sup>

The nature of the colourless modifications which are obtained by hydrolytic dissociation from both cyanin and cyanidin is not very clearly understood. In the case of cyanin chloride, it is found<sup>3</sup> that decolorization takes place when the chloride is heated for a short time in dilute alcohol at 80° C. The decolorized substance has properties resembling those of a yellow flavonol pigment; it is soluble in ether; colourless in acid solution, yellow in alkaline solution; from acid solutions it can be extracted with ether, from which it can be removed by shaking with alkali. On boiling with acids the colourless variety is reconverted into the ordinary coloured cyanidin salt.

Everest<sup>4</sup> suggests that cyanin chloride exists in solution as an equilibrium mixture of (I.)\* and (II.), and that one set of conditions favours the stability of (I.), whilst under other conditions (II.) is the more stable form.



<sup>1</sup> Wilstätter and Mieg, *Annalen*, 1915, 408, 125.

<sup>2</sup> Willstätter and Everest, *Annalen*, 1913, 401, 229.

<sup>3</sup> Everest, *Proc. Roy. Soc.*, 1914, 87, [B], 444.

<sup>4</sup> Everest, *Proc. Roy. Soc.*, 1914, 87, [B], 444.

\* The glucose molecules are omitted from the formula.

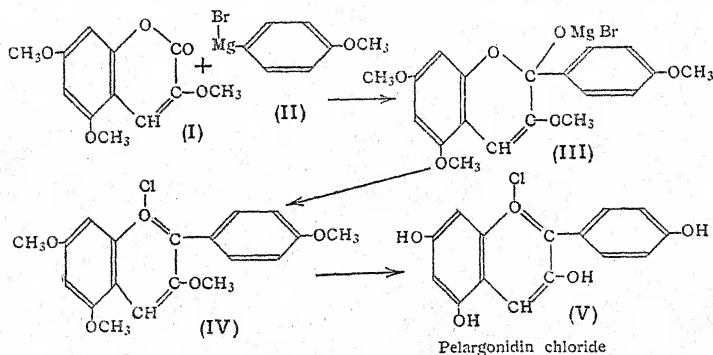
A distinction between anthocyanins and the corresponding anthocyanidins is found in the fact that amyl alcohol does not extract the former from acid solutions; but if the solution be heated so as to hydrolyse the anthocyanins to anthocyanidin, the latter passes into amyl alcohol readily.<sup>1</sup>

### 5. The Synthesis of Pelargonidin

The flowers of the scarlet perlargonium are found to contain an anthocyanin which has been named pelargonin. This substance when isolated in the form of its chloride is shown to have the composition  $C_{27}H_{31}O_{15}Cl$ , and to contain, in addition, four molecules of water of crystallization.

On hydrolysis it proves to be a glucoside, and yields two molecules of glucose and one molecule of a substance pelargonidin chloride, akin to cyanidin chloride, and having the composition  $C_{15}H_{11}O_5Cl$  with one molecule of water of crystallization.

Pelargonidin<sup>2</sup> has been synthesized in the following manner: 3:5:7-trimethoxycoumarin (I.) is allowed to interact with magnesium anisyl bromide (II.). When the intermediate compound (III.) is hydrolysed with hydrochloric acid it yields anisyltrimethoxyphenopyrylium chloride (IV.), which, after demethylation with hydriodic acid and treatment with hydrochloric acid, produces a substance (V.), indistinguishable chemically or spectroscopically from natural pelargonidin:



<sup>1</sup> Willstätter and Everest, *Annalen*, 1913, 401, 205.

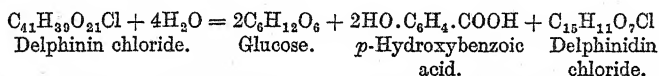
<sup>2</sup> Willstätter and Zechmeister, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 34, 886.

Another synthesis has been devised by Robertson, Robinson, and Sugiura.<sup>1</sup>

### 6. The Constitutions of Delphinin and Delphinidin

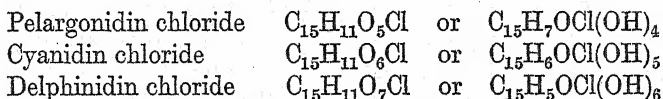
The anthocyanin of the larkspur is termed delphinin<sup>2</sup> and with it a slightly more complex field is entered. A glance at the formula of delphinin chloride:  $C_{41}H_{39}O_{21}Cl$ , shows that it has a molecular weight of 902 as compared with 646 for cyanin chloride; so it is evident that the former substance must contain some heavy radicle in addition to those found in cyanin or pelargonin.

Hydrolysis of delphinin proves the correctness of this. In addition to the products which might be expected (glucose and delphinidin) two molecules of *p*-hydroxybenzoic acid make their appearance; so that the equation for the reaction may be written thus—



It appears from this that delphinin, like the other anthocyanins, is a glucoside; but that two of its hydroxyl radicles are esterified with *p*-hydroxybenzoic acid. Which of the hydroxyl groups are thus affected is not known definitely; but by analogy with populin (benzoysalicin) it is assumed that the benzylation takes place in the glucose chain and not in the delphinidin portion of the molecule.

The next stage in the deduction of delphinin's constitution is made by comparing the formulæ of pelargonidin, cyanidin, and delphinidin chlorides:—



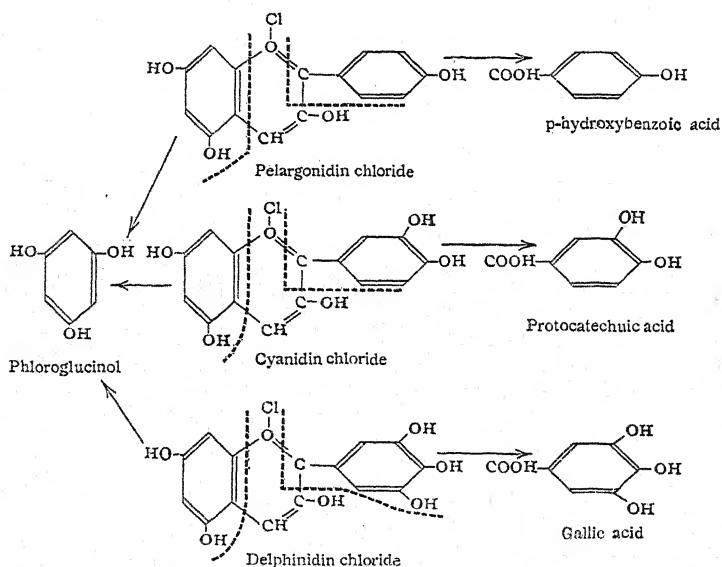
The comparison suggests that the difference between cyanidin and delphinidin may lie in the presence of an extra hydroxyl group in the delphinidin molecule.

Confirmation of this view is obtained when the results of heating the three compounds with alkali are considered. All

<sup>1</sup> Robertson, Robinson, and Sugiura, *J.*, 1928, 1533.

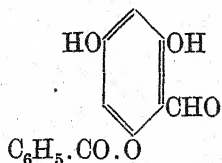
<sup>2</sup> Wilstätter and Mieg, *Annalen*, 1915, 408, 61.

three yield phloroglucinol; so that they contain a common grouping. In addition to the trihydric phenol, however, pelargonidin yields *p*-hydroxybenzoic acid; cyanidin produces protocatechuic acid; whilst delphinidin gives rise to gallic acid. From this it appears a reasonable deduction that the portion of the molecule which produces *p*-hydroxybenzoic acid in the case of pelargonidin is the same in nature as that which gives rise to gallic acid from delphinidin. A comparison between the two established formulæ and the one suggested for delphinidin will make the matter clear :



### 7. A General Method of Synthesising Anthocyanidins

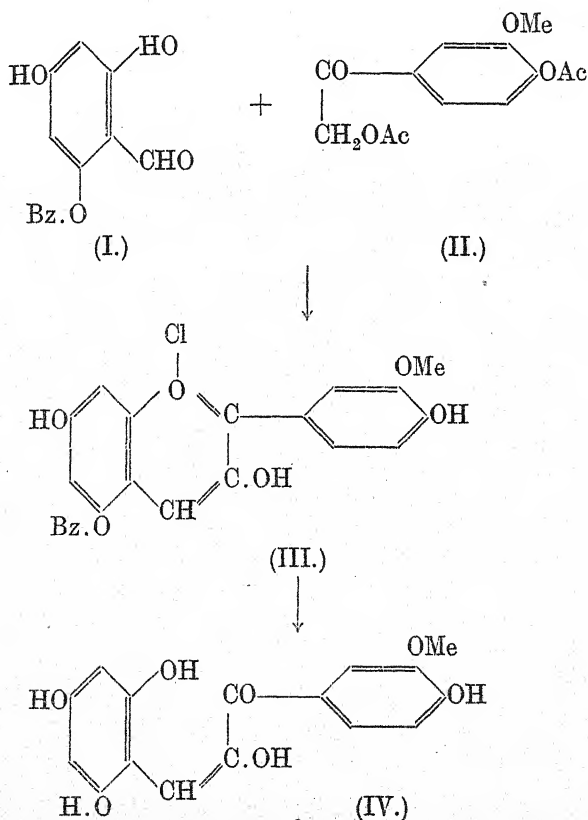
When phloroglucin-aldehyde is monobenzoylated by the Baumann-Schotten method,<sup>1</sup> it yields 2-benzoyloxy-4:6-dihydroxy-benzaldehyde :



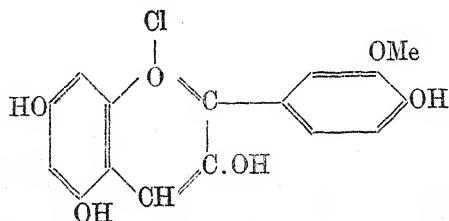
<sup>1</sup> Robinson and Struthers, *J.*, 1928, 1455.

This substance is condensed with acetylated derivatives of substituted  $\omega$ -hydroxy-acetophenones by the use of hydrogen chloride in ethyl acetate (or alcoholic ethyl acetate) solution; and the acetyl groups are removed by hydrolysis. The substances are then hydrolysed with aqueous-alcoholic sodium hydroxide to remove the benzoyl radicle; and the anthocyanidins are produced by a final treatment with hydrochloric acid.

One example of the system will suffice. By condensing 2-benzoyloxy-4:6-dihydroxy-benzaldehyde (I.), with  $\omega$ -4-di-acetoxy-methoxy-acetophenone, (II.), the reaction yields 5-O-benzoyl-peonidin chloride (III.). Alkaline hydrolysis removes the benzoyl group and simultaneously opens the pyrylium ring, yielding (IV.). Finally, by means of hydrochloric acid, the ring is reclosed, and peonidin chloride, (V.), is obtained.

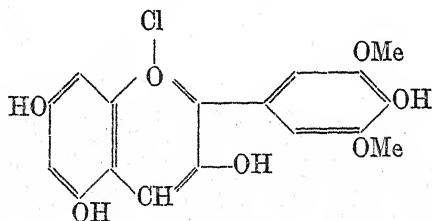






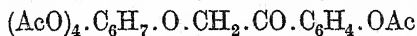
(V.) Peonidin chloride.

By selecting the appropriate derivative of acetophenone, this method can be applied to the synthesis of various anthocyanidins.<sup>1</sup> Thus  $\omega$ -3 : 4-triacetoxy-acetophenone yields cyanidin chloride; and  $\omega$ -4-diacetoxy-acetophenone gives pelargonidin chloride. Malvidin chloride (syringidin chloride), which occurs naturally in the flowers of the wild mallow, has been produced by using  $\omega$ -acetoxy-4-benzoyloxy-3 : 5-dimethoxy-acetophenone :—



Malvidin chloride.

An actual synthesis<sup>2</sup> of a flower pigment was first accomplished in the case of callistephin chloride, which is derived from the summer aster.<sup>3</sup> By acting on a mixture of  $\omega$ -hydroxy-4-acetoxy-acetophenone and O-tetra-acetyl- $\alpha$ -glucosidyl bromide\* with dry silver carbonate in benzene solution,  $\omega$ -O-tetra-acetyl- $\beta$ -glucosidoxy-4-acetoxy-acetophenone was obtained :—



When condensed with O-benzoyl-phloroglucin-aldehyde, it yielded 3-O-tetra-acetyl- $\beta$ -glucosidoxy-7-hydroxy-5-benzoyloxy-

<sup>1</sup> Robinson and others, *J.*, 1928, 1526, 1533, 1537, 1541; 1930, 793.

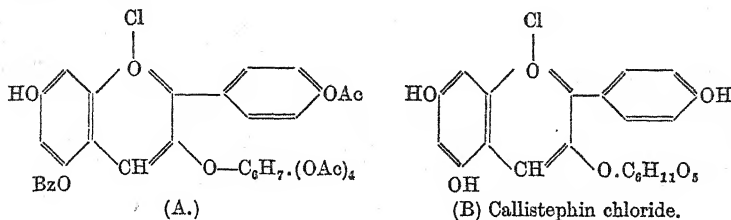
<sup>2</sup> Robertson and Robinson, *J.*, 1926, 1713; 1927, 242, 1710.

<sup>3</sup> Willstätter and Burdick, *Annalen*, 1916, 412, 149.

\* Note.—The  $\alpha$ -sign here does not refer to a relationship to  $\alpha$ -glucose, but indicates that this one of two isomers has the greater dextrorotation. This compound, in fact, has the same configuration as  $\beta$ -glucose and no Walden inversion has occurred during the formation of the  $\beta$ -glucosidoxy-derivative.<sup>4</sup>

<sup>4</sup> Hudson, *J. Amer. Chem. Soc.*, 1909, 31, 66.

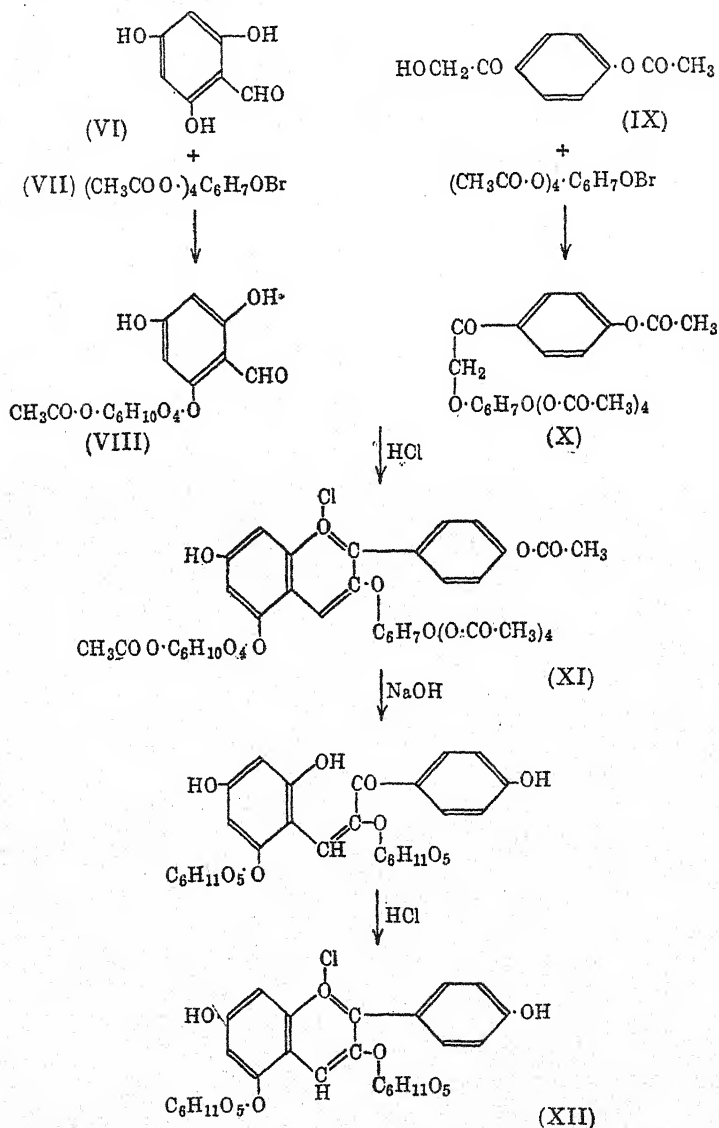
4'-acetoxy-flavylium chloride (A); from which callistephin chloride (B) was obtained by hydrolysis with aqueous alkali and subsequent treatment with acid.



### 8. The Synthesis of an Anthocyanin

The chemistry of the anthocyanins was taken a stage further when the diglucosides, malvin, hirsutin, cyanin, peonin and pelargonin chlorides were synthesized and shown to be identical with the substances from natural sources. The synthesis of pelargonin chloride may be taken to illustrate the methods employed, and constitutes a great improvement on the older processes. Phloroglucinaldehyde (VI.) and O-tetra-acetyl- $\alpha$ -glucosidyl bromide (VII.) were dissolved in acetone and cooled in ice. To this solution aqueous potassium hydroxide was added in small portions with vigorous shaking. After the partial elimination of impurities the monoglucosidic and diglucosidic substances were separated by treatment of the ether solution with sodium carbonate solution. The alkaline extract of the monoglucoside was acidified with hydrochloric acid and the whole extracted with ether. The solid finally obtained by repeated fractional crystallization from methyl alcohol yielded 2-O-monoacetyl- $\beta$ -glucosidylphloroglucinaldehyde (VIII.) and the 2-O-tetra-acetyl-derivative, three acetyl groups having been removed from the former by hydrolysis during the operations. The other compound required,  $\omega$ -O-tetra-acetyl- $\beta$ -glucosidoxy-4-acetoxyacetophenone (X.), was prepared from  $\omega$ -hydroxy-4-acetoxyacetophenone (IX.) and O-tetra-acetyl- $\alpha$ -glucosidyl bromide by condensation in anhydrous benzene. The aldehyde (VIII.) and acetophenone (X.) derivatives were then dissolved in ethyl acetate and saturated with dry hydrogen chloride at 0°C. The flavylium salt (XI.) formed was isolated and dissolved in sodium hydroxide solution. After standing for a time the alkaline

solution was acidified with hydrochloric acid. Pelargonin chloride (XII.) crystallized out and proved to be identical with the natural substance.<sup>1</sup> The structures may be represented as follows :—



<sup>1</sup> Robinson and Todd, *J.*, 1932, 2293, 2299, 2488.

## 9. Other Anthocyanins

Mention must now be made of some other plant pigments which contain the skeletons we have already described.

In the summer aster occurs an anthocyanin asterin, which hydrolyses into cyanidin and glucose.<sup>1</sup>

The anthocyanin of the winter aster is chrysanthemin, derived from glucose and cyanidin. Cyanidin also forms the foundation for the colours of *Zinnia elegans*, *Gaillardia bicolor*, *Helenium autumnale*, *Gladiolus Tulipa Gesneriana*, *Tropæolum majus*, *Rubus rubrum*, the raspberry, and the berry of the mountain ash.<sup>2</sup> The cherry contains keracyanin, built up from cyanidin, glucose, and rhamnose; whilst the sloe owes its colour to prunicyanin, which is formed from cyanidin, rhamnose, and some as yet unidentified hexose.<sup>3</sup> The plum also contains a cyanidin glucoside.<sup>3</sup>

Peonin, the anthocyanin of the peony, belongs to the cyanidin series.<sup>4</sup> It is a diglucoside of peonidin. Another cyanidin derivative is idaein,<sup>5</sup> the anthocyanin of the whortleberry. It differs from the usual type of anthocyanin in that it is a galactoside and not a glucoside.

The poppy<sup>6</sup> contains two anthocyanins, one of them, meco-cyanin, being a cyanidin derivative, whilst the other resembles the glucosides of delphinidin.

Turning to delphinidin derivatives, it is found that the pansy owes its colour to the anthocyanin violanin,<sup>7</sup> which on hydrolysis yields delphinidin, rhamnose, and some as yet unidentified hexose, though these three products do not occur in equimolecular quantities in the reaction mixture. Monomethyl ethers of delphinidin are found in myrtillin,<sup>8</sup> the anthocyanin of bilberries, and petunin,<sup>9</sup> the anthocyanin of petunias. A dimethyl ether of delphinidin has been isolated from oenin,<sup>10</sup> the anthocyanin of grapes.

<sup>1</sup> Willstätter and Burdick, *Annalen*, 1916, 412, 149.

<sup>2</sup> Willstätter and Bolton, *Annalen*, 1916, 412, 136.

<sup>3</sup> Willstätter and Zollinger, *Annalen*, 1916, 412, 164.

<sup>4</sup> Willstätter and Nolan, *Annalen*, 1915, 408, 136.

<sup>5</sup> Willstätter and Mallison, *Annalen*, 1915, 408, 15.

<sup>6</sup> Willstätter and Weil, *Annalen*, 1916, 412, 231.

<sup>7</sup> Willstätter and Weil, *Annalen*, 1919, 412, 178.

<sup>8</sup> Willstätter and Zollinger, *Annalen*, 1915, 408, 83.

<sup>9</sup> Willstätter and Burdick, *Annalen*, 1916, 412, 217.

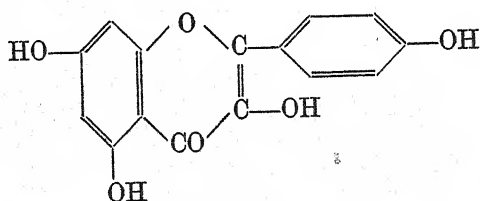
<sup>10</sup> Willstätter and Zollinger, *Annalen*, 1915, 408, 83.

Finally, mention may be made of a glucoside ampelosin, which occurs in the wild vine. Its constitution has not yet been determined.

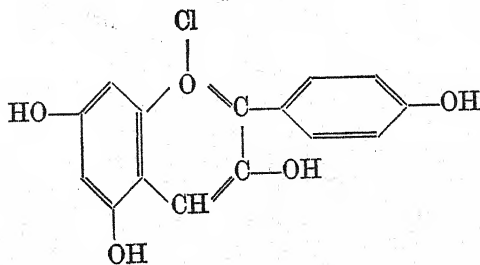
### 10. *The Anthocyanins and the Flavones*

It may be of interest to point out the similarity in structure which can be traced between the flower pigments and the natural dyes occurring in plants; for the close resemblance in the skeletons of the two classes may throw light in the future upon the mode in which both types are built up within the organism. Such a similarity can hardly be regarded as due to mere chance.

Taking kampherol as a flavone representative, and comparing it with pelargonidin chloride as a typical example of the anthocyanins, it will be seen that they bear a striking resemblance to one another in general structure:



Kampherol.



Pelargonidin chloride.

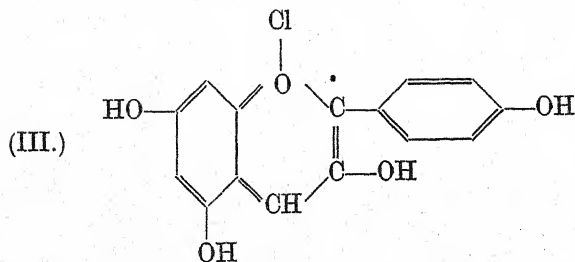
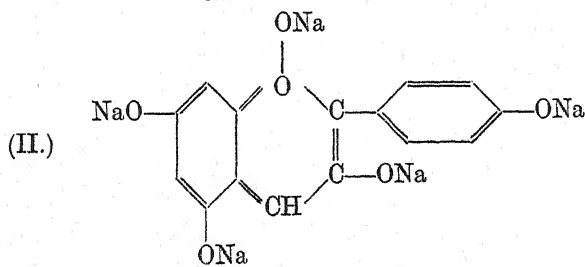
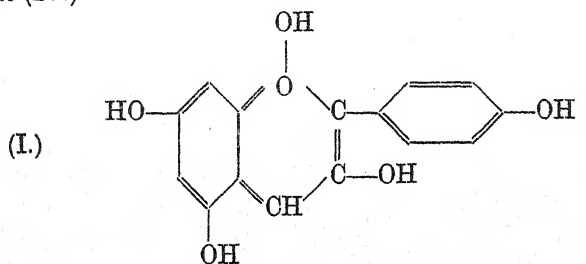
The only difference between them is to be found in the heterocyclic nucleus; the one is a true pyrone, whilst the other contains a  $-\text{CH}=\text{}$  group instead of the carbonyl radicle; and its structure is therefore more benzenoid in character. This difference is, of course, exhibited in their salts; the kampherol salts, being derived from a true pyrone, are easily hydrolysed even in the sap of plants; whilst the salts of anthocyanins are sufficiently stable to exist without decomposition in the vegetable structure.

Compounds analogous to the anthocyanins have been synthesized,<sup>1</sup> by using the Perkin-Robinson<sup>2</sup> method for the synthesis of pyrylium salts from *o*-hydroxybenzaldehyde and compounds containing the  $-\text{CH}_2\text{CO}-$  group.

### 11. *The Origin of Colour Variation in Plants*

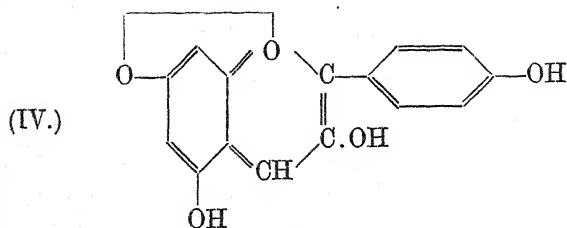
In view of the strong family resemblance between the various plant pigments, it may be interesting to indicate the manner in which such closely related compounds might give rise to such gradations of tint as are shown in the flowers.

An examination of the structure of pelargonidin (I.) will show that it is capable of yielding various types of derivatives: metallic salts like (II.), oxonium salts like (III.), and internal ethers like (IV.):—

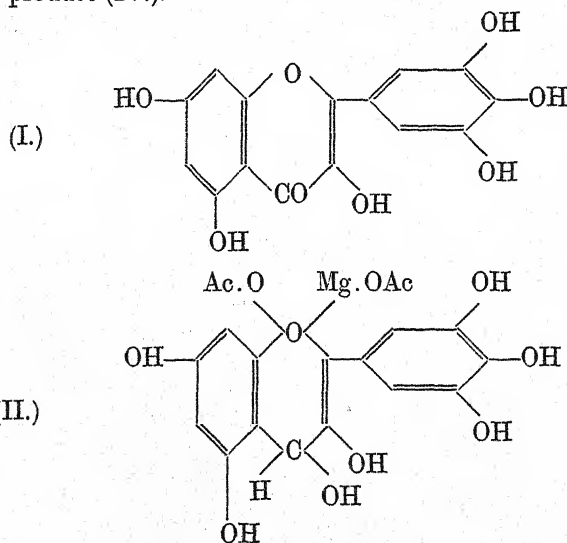


<sup>1</sup> Pratt and Robinson, *J.*, 1922, 121, 1577.

<sup>2</sup> Perkin and Robinson, *P.*, 1907, 19, 149.




The importance of metallic derivatives of the anthocyanins has been emphasized by some work on the subject.<sup>1</sup> Reduction of a flavone derivative by means of a metal and a *mineral* acid leads to a production of a red compound; but when magnesium and an *organic* acid such as acetic acid are employed in presence of mercury, the colour of the product is found to diverge from the normal red tint. Thus when myricetin (I.) is reduced in this way, it yields green compounds which have the composition  $C_{18}H_{11}O_8 \cdot Mg \cdot OAc$ ,  $[Mg(OAc)_2]$ . The reaction apparently proceeds in stages. In the first stage, the phenopyrylium derivative (II.) is formed; which then passes by elimination of acetic acid into (III.), which finally unites with magnesium acetate to produce (IV.).



<sup>1</sup> Shibata, Shibata and Kasiwagi, *J. Amer. Soc.*, 1919, 41, 208; compare Karrer and Widmer, *Helv. Chim. Acta*, 1927, 10, 729.



(III.)



Chemical structure (III) shows a central magnesium atom (Mg) coordinated by two acetate groups (OAc) and two phenolate oxygen atoms. The phenolate groups are part of a larger structure consisting of two benzene rings connected by a central carbon atom. This central carbon is also bonded to two hydroxyl groups (OH). The left benzene ring has two hydroxyl groups (OH) at the 2 and 6 positions. The right benzene ring has two hydroxyl groups (OH) at the 2 and 6 positions. The entire structure is labeled (III.)

(IV.)

$$\left[ \begin{array}{c} \text{Mg} \cdot \text{OAc} \\ \text{OH} \\ \text{HO} - \text{C}_6\text{H}_3 - \text{O} - \text{C}(\text{OH})_2 - \text{C}_6\text{H}_3 - \text{O} - \text{C}(\text{OH})_2 - \text{C}_6\text{H}_3 - \text{OH} \\ \text{OH} \end{array} \right] [\text{Mg}(\text{OAc})_2]_n$$

If, instead of myricetin itself, a rhamnoside derivative, myricitrin, is used, the resulting product is a deep blue substance containing four molecules of magnesium acetate.

The difference between the reaction-products when mineral and organic acids are employed has been traced to the fact that the radicle —Mg. Cl is replaced by a chlorine atom if hydrochloric acid is present in quantity; so that the end-product is the red oxonium chloride.

Basing themselves upon these results, Shibata, Shibata and Kasiwagi suggested that metallic complex salts of the type:—

$$\left[ \text{(Sugar)} \left( \begin{array}{c} \text{MX} \\ | \\ \text{O} \\ | \\ \text{C} \\ | \\ \text{OH} \end{array} \right) \begin{array}{c} \text{C}_6\text{H}_5 \\ | \\ \text{OH} \end{array} \right] [\text{MX}_2]$$

are important factors in flower coloration and give rise to the "blue" anthocyanins. The metallic atoms which they contain (indicated by M in the formula) are probably calcium and magnesium. The "violet" and "red" pigments are assumed to be

complex salts containing fewer hydroxyl groups than the "blue" ones; or to be mixtures of the "blue" compounds with a certain quantity of the red oxonium salts which have been formed from the "blue" derivatives by decomposition with acids.

The existence of these various types would be conditioned by the nature of the sap in the neighbourhood of the pigment; and as the sap must obviously be more highly concentrated the nearer we go to the evaporating surface of the petals, it is evident that variations in the structure of the pigment must be expected. Again, the sap in certain parts of the plant may be more alkaline than in others; and as the cyanidins are indicators, it is clear that their tint will be affected by this factor also.

## CHAPTER XI

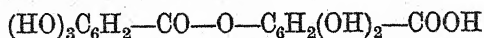
### THE DEPSIDES AND TANNINS

#### A.—HISTORICAL

GALL-NUTS contain, in proportions varying up to 50 per cent., a material termed tannin, which can be extracted from the powdered nuts by means of organic solvents. Obtained in this way, it is a colourless, amorphous substance with an astringent taste. It is easily soluble in water, slightly soluble in alcohol, and almost insoluble in ether. From its aqueous solutions it is precipitated by mineral acids, common salt, or gelatine; and it can be removed from water by dipping animal membranes into the solution. It is optically active, and has an electrical conductivity, though of a low degree. With ferric chloride it produces a blue coloration, which is utilized in the manufacture of certain inks. On treatment with dilute acids, it gives a large yield of gallic acid,  $(\text{HO})_3\text{C}_6\text{H}_2\cdot\text{COOH}$ .

As a result of extensive researches carried out in the middle of last century, Strecker<sup>1</sup> came to the conclusion that tannin was a compound containing three gallic acid nuclei and one glucose nucleus; and on these assumptions tannin would have the formula,  $\text{C}_{27}\text{H}_{22}\text{O}_{17}$ . The glucose portion of the molecule would account for the optical activity of tannin; whilst the presence of the gallic acid nuclei would explain the detection of this acid among the tannin hydrolysis products.

At a later date, the dehydration of gallic acid was attained by means of silver nitrate, arsenic acid,<sup>2</sup> and phosphorus oxy-chloride;<sup>3</sup> and the product was found to be a substance termed digallic acid, which is produced by the carboxyl group of one gallic acid molecule becoming esterified by a hydroxyl group belonging to a second gallic acid molecule:



<sup>1</sup> Strecker, *Annalen*, 1852, 81, 248; 1854, 90, 328.

<sup>2</sup> Löwe, *Jahresbericht f. Chemie*, 1867, 446; 1868, 559.

<sup>3</sup> Schiff, *Ber.*, 1871, 4, 232, 967; 1879, 12, 33; *Annalen*, 1873, 170, 143.

Schiff believed that this substance, with the simple formula  $C_{14}H_{10}O_9$ , was actually a synthetic form of tannin. This structure, of course, left out of account the optical rotatory power of natural tannin; but it must be borne in mind that at that date the analyses which had been made of tannin showed very marked differences in the percentage of sugar detected; and, in view of the amorphous character of the material, it seemed quite possible that the optically active substance was merely a variable impurity in the tannin preparations and not an indispensable constituent.

This conception of tannin lasted almost unchallenged for a quarter of a century; but in 1897, Walden<sup>1</sup> made a comparison between the properties of digallic acid and natural tannin, which proved beyond doubt that the two materials differed in absorption spectra, electrical conductivity, and behaviour towards arsenic acid. Attempts were made to resuscitate the digallic acid formula by assuming that natural tannin was a mixture of digallic acid with some other tannin-like material (leuco-tannin) possessing optical activity; but they are of no importance at the present day.

Thus in the early years of the present century, our knowledge of the tannin constitution was hardly more exact than it had been fifty years before. In the standard textbooks, the references to the subject, vague as they were, dealt with the material as a mixture.<sup>2</sup> The analytical method of investigation had failed to clear up the subject or even to settle whether tannin should be regarded as optically active *per se*. But now a new figure came upon the scene. Once again Emil Fischer was preparing his synthetic weapons for the attack upon yet another group of the naturally occurring compounds; and, for the last time, he was to bring clarity into a perplexing problem.

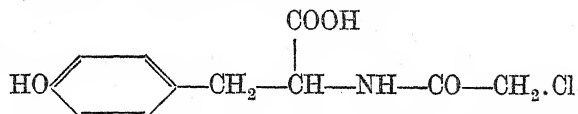
By the year 1906, Fischer's interest in the polypeptides was fading out. He had laid the foundations of the subject firmly enough for other men to build upon; and it was time to turn his mind to some other field. For two years he was attracted by the problem of the Walden Inversion, which had come to his notice in connection with his researches upon the amino-acids; but this was, to him, merely an interlude between his

<sup>1</sup> Walden, *Ber.*, 1897, 30, 3151; 1898, 31, 3167.

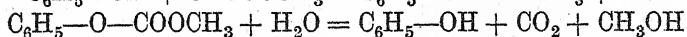
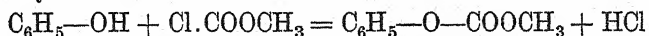
<sup>2</sup> See, *inter alia*, Richter, *Organische Chemie*, vol. ii., p. 333 (1913).

self-appointed tasks in the great division of the natural products. He was already looking round him in search of a fresh field, when an investigation carried out in his own laboratory set him on the track for which he was seeking.

In the preparation of glycyl-tyrosyl-glycine, it had been necessary to obtain chloracetyl-tyrosine :

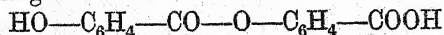


and then convert this into the acyl chloride. Now phosphorus chloride had the disadvantage that it affected not only the carbonyl group but the phenolic hydroxyl radicle as well. Fischer therefore sought for some means of protecting the hydroxyl radicle by introducing a group which could be easily eliminated at a later stage in the synthesis ; and this protective agent he discovered in the carbomethoxy radicle. By acting on phenols with chloroformic methyl ester, the phenolic hydrogen atom can be replaced by the group  $\text{---COOCH}_3$  ; and, when it is necessary, the hydroxyl group can be regenerated by a mild hydrolytic action :



It will be recalled that Fischer had already, in his polypeptide syntheses, utilized chloroformic ester in the protection of amino-groups ; but he had to abandon its use on account of the fact that the  $\text{---COOEt}$  group could not be split off again in order to regenerate the original amino-radicle. This difficulty, obviously, does not make its appearance in the case of the phenols.

Tyrosine, with its reactive carboxyl radicle and its protectable hydroxyl group, gave Fischer the clue for which he had been searching. The polypeptide investigations had impressed on his mind the manner in which natural products may be built up by linking together in a chain a series of molecules, each of which contains an acidic and a basic radicle. Now, in the hydroxy-benzoic acids, he glimpsed the possibility of a fresh series of chain-compounds obtained by esterifying the carboxyl group of one acid molecule with the hydroxyl group belonging to a second ring :



The occurrence of digallic acid in the decomposition products of tannin showed that chains of this description actually<sup>1</sup> did occur in nature. Fischer had found his new subject for investigation; and, as was his custom, he set about developing it in the broadest manner from the synthetic side.

The work mentioned in the foregoing account of the development of the subject was concerned with the depside type of tannin. In addition to the depside or hydrolysable tannins there is another group of materials characterized by their resistance to hydrolysis. In this latter group the phlobatannins are the most important members, and work on these substances has to a great extent centred round the catechins and allied synthetic compounds.

#### B.—THE NATURE OF THE DEPSIDES<sup>1</sup>

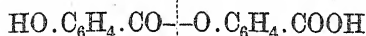
As so often happened with Fischer's vast and intricate researches, his entry into a fresh field soon demanded the devising of a special nomenclature<sup>2</sup> for the compounds which his ingenuity evolved. Since the substances undoubtedly had a kinship with tannin, Fischer coined the term *depside* (from δέψειν, to tan) as a class-name for the whole group. The word had the additional advantage of a likeness to "peptide"; and thus carried with it a suggestion of the similarity in the catenarian construction of the two types of compound. The remainder of the nomenclature followed on the lines of the polysaccharides and the polypeptides, being based upon the number of hydroxy-acid radicles united in the chain. When two hydroxy-acid radicles are coupled together, the compound is a *didepside*. Three coupled radicles compose a *tridepside* chain; and four radicles, when united, make a *tetradepside*. The following formulæ will make the matter clear, as the dotted lines show the division between the radicles. The depsides chosen are assumed to be derived from a hydroxy-benzoic acid,  $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$ .

<sup>1</sup> Fischer's collected papers in this branch of chemistry have been republished under the title *Untersuchungen über Depside und Gerbstoffe* (1919). A summary of his work is to be found in his two lectures on the subject (*Ber.*, 1913, 46, 3253; 1919, 52, 809). The personal side of the matter is very well treated in Hoesch's *Emil Fischer: Sein Leben und sein Werk* (1921).

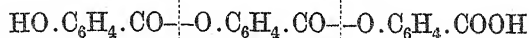
<sup>2</sup> Fischer and Freudenberg, *Annalen*, 1910, 372, 32.



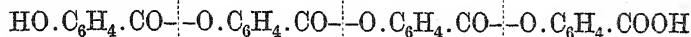
Example of a didepside :



Example of a tridepside :



Example of a tetradepside :



The terminology for individual compounds follows the lines already made familiar by the polypeptides. Thus the didepside shown above, if derived from *p*-hydroxybenzoic acid, would be termed *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid. The tridepside would be described as di-*[p*-hydroxybenzoyl]-*p*-hydroxybenzoic acid. The tetradepside would have the name : tri-*[p*-hydroxybenzoyl]-*p*-hydroxybenzoic acid.

### C.—SOME FACTORS WHICH INFLUENCE DEPSIDE FORMATION

At the first glance, the depsides seem to furnish a close parallel to the polypeptides, since in the syntheses of the two classes the analogous processes of amide-formation and esterification are used. Closer inspection reveals, however, that there are marked differences between them ; and that in almost every case the disadvantage lies with the depsides.

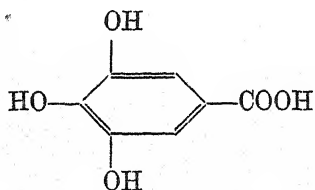
In the amino-acids from which the polypeptides are built up, the two interacting groups are markedly different in character, the acidity of the carboxyl radicle meeting its complement in the basic nature of the amino-group. In the depsides, however, the acidic carboxyl has to be forced into combination with the semi-acidic hydroxyl group of a phenol, which is not nearly so simple an operation as amide formation. It seems not improbable that this factor in itself is sufficient to account for the subordinate rôle in nature which is played by the depsides. There is not, in the depside molecule, that regular alternation of basic and acidic radicles which seems to make the almost infinite extension of the polypeptide chain a possibility.



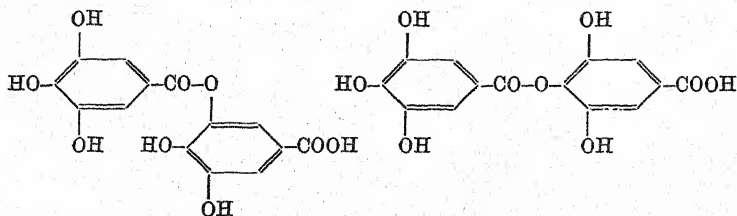
Again, in the polypeptides synthesized by Fischer, the structural difficulties were reduced to a minimum since each amino-acid molecule contained only one carboxyl and one amino-radicle. Among the depsides, however, the isomerism due to the phenyl nucleus introduces complications in more than one form.

In the first place, the simplest phenolic acid exists in three isomeric forms; and it was found that these acted quite differently in depside formation. Para-hydroxybenzoic acid underwent depside formation with comparative ease; the meta-acid showed less readiness in reaction; whilst the acid with the carboxyl and hydroxyl radicles in the ortho-positions could only be made to form depsides with difficulty. Evidently the simplicity of the syntheses is governed by the nature of the reagents to a very considerable extent.

Secondly, an even greater difficulty arises when the case of the polyhydroxy-benzoic acids is examined. Take gallic acid



as an example. Here there are two hydroxy-groups in the *meta*-position to the carboxyl group and the remaining hydroxyl is in the *para*-position. It is obvious that if two molecules of this substance interact, the carboxyl group of one molecule may attach itself either in the *meta*- or in the *para*-position to the carboxyl of the second molecule, leading to the production of a mixture\* of the two compounds shown below:



\* A somewhat analogous difficulty in the polypeptide syntheses is found in the formation of mixtures of non-antipodic forms when *dl*-amino acids are employed.

In order to avoid the production of this mixture, which in the case of higher depsides would be difficult to resolve into its separate constituents, it is necessary to shield certain hydroxyl groups from the action of the acid, leaving open to its attack only one hydroxyl group in a known position in the structure. After the esterification is completed, these shielded hydroxy groups must then be brought back to their original condition.

A final difficulty, which presents itself in certain cases, is caused by the possibility of intramolecular rearrangements taking place; but this point can best be dealt with later in the present chapter.

#### D.—THE SYNTHESIS OF DEPSIDES

From what was mentioned in the foregoing section, it will be clear that in the synthesis of the depsides there are three processes involved: (a) the protection of those hydroxyl groups which are not to be attacked by the carboxyl radicle; (b) the coupling reaction; and (c) the regeneration of the shielded hydroxyl groups. It will be convenient to deal with these in turn.

(a) *The Protection of Hydroxyl Groups.*—In this problem three factors have to be taken into account. The shielding group must be easily introduced; it must be readily removed; and, if possible, it should improve (or not deteriorate) the power of crystallization of the substance under examination. The first two factors limit the choice, so far as depsides are concerned, to acyl radicles such as acetyl, benzoyl, and the carbomethoxy group. The molecular weight of depsides being so high, the introduction of a heavy radicle like benzoyl is not advantageous; so the final selection is limited to the acetyl and carbomethoxy groups; and in the final depside syntheses the acetyl radicle was found to yield better crystalline derivatives than the carbomethoxy group.

It is comforting to lesser chemists to find that even Fischer could take the wrong track on at least one occasion. A study of the literature of the subject had convinced him<sup>1</sup> that the removal of the acetyl group from phenols required strong reagents such as boiling alkali; and as such reagents would naturally tend to hydrolyse the depside junctions, he avoided the acetylation method of shielding until quite far on in his researches. When driven back to it by force of circumstances, he found that

<sup>1</sup> Hoesch, *Emil Fischer*, p. 456; *Fischer, Ber.*, 1919, 25, 809.

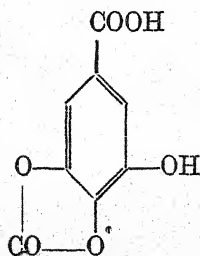
he had been misled; and in his later work he adopted the introduction of acetyl groups as the simplest and most satisfactory method of protection for his hydroxyl radicles.

In practice the acetylation of the phenolic acids was carried out by shaking the acid with acetic anhydride in presence of zinc chloride, dimethylaniline, or pyridine. This leads to complete acetylation; and thereafter one of the hydroxyls can be freed again by hydrolysis with potassium carbonate solution. The identity of the particular hydroxyl group set free is established by converting it into a methyl ether by means of diazomethane, hydrolysing away the remaining acetyl radicles and identifying the ether thus produced.

For example, gallic acid is first converted into triacetyl-gallic acid. By controlled hydrolysis, this is changed into 3, 5-diacetyl-gallic acid, which is then ready for depside synthesis, owing to its single free hydroxyl group. The identity of the 3, 5-diacetyl compound is established by methylating the free hydroxyl with diazomethane and hydrolysing the two acetyl radicles, when the product is found to be 4-methoxy-3, 5-dihydroxy-benzoic acid.

The second protection method consists in shaking the phenolic acid in cold alkaline solution with chloro-formic methyl ester and acidifying after the reaction has run its course. Here, as in the foregoing case of acetylation, all the hydroxyl groups are attacked by the reagent; and in order to free one of them for depside synthesis a partial hydrolysis with alkali or ammonia is necessary.

A third protection method was used by Fischer in the case of polyhydroxy-compounds having two hydroxyls in the *ortho*-position. Carbonyl chloride was allowed to act upon the polyphenol, with the result that a ring was formed at the two *ortho*-positions. Gallic acid, for example, yields the compound shown below:

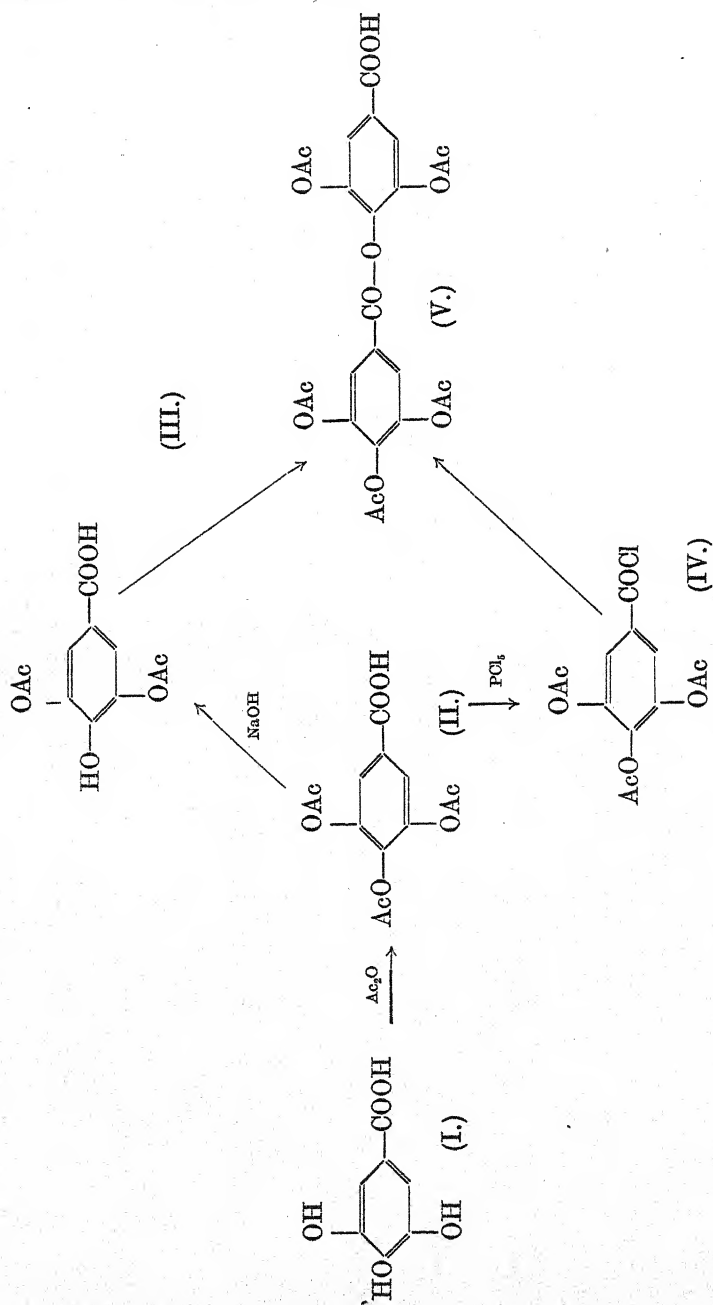


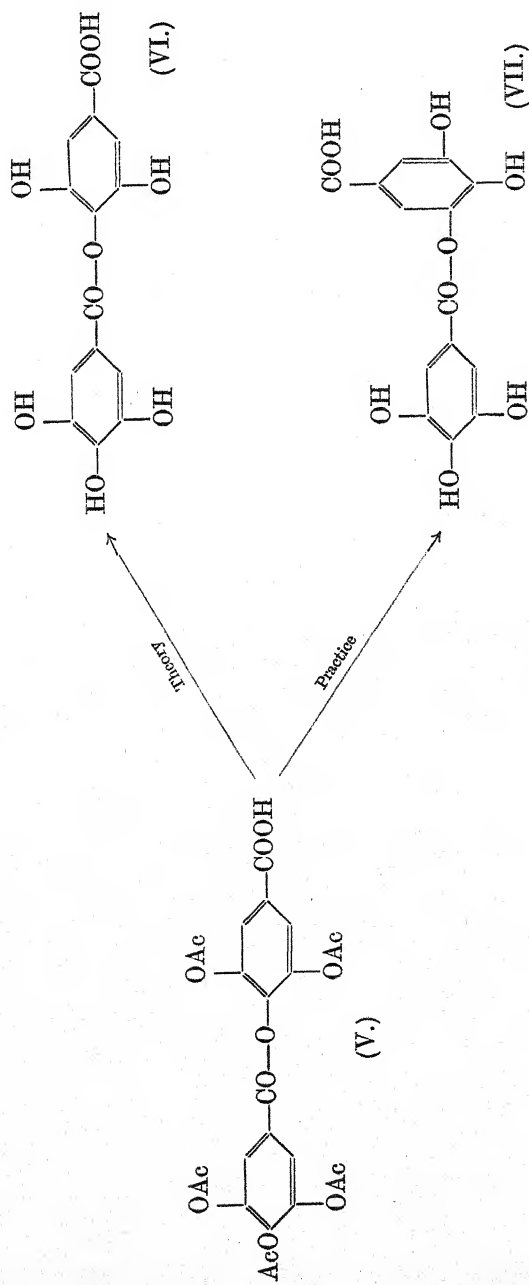
(b) *The Coupling of Nuclei.*—It will be recalled that in the polypeptide work, Fischer employed by preference the acyl chlorides as reagents to act upon the amino-group of the amino-acids during the process of chain-formation. In the field of the depsides the catenation was brought about in an analogous manner by the action of acyl chlorides upon the phenolic acids. The chlorides were readily obtained by the action of phosphorus pentachloride upon the carboxyl group after the hydroxyl radicles of the molecule had been protected as has already been described. The interaction between acyl group and phenolic hydroxyl took place readily in acetone solution in presence of alkali, dimethylamine, or aluminium chloride; and by subsequent addition of dilute mineral acid, the depside was precipitated.

(c) *The Regeneration of the Hydroxyl Group.*—After the completion of the coupling, the protective acetyl groups are easily removed by the action of alkali, even at ordinary temperatures. Ammonia is also a reagent sufficient for the purpose; and if the temperature be raised, sodium acetate will effect the deacetylation rapidly. By using different quantities of alkali, the hydrolysis can be stopped at fixed stages instead of being run through to completion in one operation. For the removal of the carbomethoxy-group, normal alkali solutions are used in most cases; sometimes sodium carbonate solution can be employed with advantage; and in certain cases ammonia in presence of pyridine has proved a satisfactory agent.

At this point, it seems of interest to trace the steps in the synthesis of a depside: digallic acid. For the sake of clearness, the acetyl group is represented by the symbol Ac in the formulæ.

Gallic acid (I.) is first converted into triacetyl-gallic acid (II.). Partial hydrolysis yields 3, 5-diacetyl-gallic acid (III.), which is the phenolic compound to be used in the synthesis. The triacetyl-gallic acid (II.) is treated with phosphorus pentachloride, yielding triacetyl-galloyl chloride (IV.). The diacetyl-compound (III.) and the chloride (IV.) are then allowed to interact, with the production of the pentacetyl-digallic acid (V.), from which a depside, digallic acid, is obtained by hydrolysis of the five acetyl groups by means of alkali.

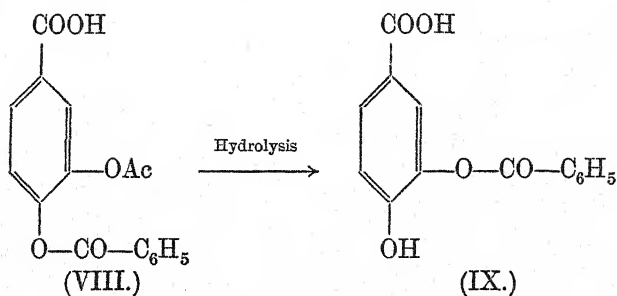




## E.—INTRAMOLECULAR CHANGE IN THE DEPSIDES

The example of depside formation given in the foregoing section was chosen to illustrate a further point which raised difficulties in the depside field. As can be seen from the formulæ, there can, apparently, be no doubt as to the constitution of the pentacetyl derivative (V.); and the natural assumption would be that, on removing the five acetyl groups by hydrolysis, the didepside (VI.) would be produced. In actual practice, however, this substance is not formed; but, instead, the end-product of the hydrolysis is the compound with the constitution (VII.). Instead of the expected *para*-digallic acid, a *meta*-digallic acid is formed.

The explanation of this apparently mysterious phenomenon was found by Fischer in a wandering of the galloyl radicle from the *para*- into the *meta*-position during the hydrolysis of the acetyl groups. This wandering is not confined to the galloyl radicle; for when the benzoyl group is substituted for the galloyl nucleus, it also wanders in precisely the same way. Further, when *p*-benzoyl-acetyl-protocatechuic acid (VIII.) is hydrolysed, the removal of the acetyl group is accompanied by a similar wandering of the benzoyl radicle, so that *m*-benzoyl-protocatechuic acid (IX.) is the end-product:



From these and other results, it appears that the phenomenon is a general one in this series of compounds.

The wandering of radicles from one atom to another is, of course, nothing new in organic chemistry. The shift of acyl groups from the oxygen to the carbon atom in acetoacetic ester



syntheses will occur to the mind of the reader at once. Among other examples might be mentioned the production of N-benzoyl-aminophenol by the reduction of O-benzoyl-o-nitrophenol;<sup>1</sup> and the conversion of O-carbethoxy-o-aminophenol into N-carbethoxy-o-aminophenol.<sup>2</sup> What makes the Fischer change so remarkable is that the wandering takes place between two hydroxyl groups, the only difference between which is their structural position in respect to the carboxyl radicle.

No explanation has yet been found for this peculiar intramolecular rearrangement, which Fischer likens to the equally unexplained case of the benzoyl derivatives of dulcitol and its acetone-derivative.<sup>3</sup>

## F.—THE LICHEN ACIDS

### 1. General

Up to the present time, the lichens are the solitary abundant natural source of depsides. If Schwendener's views be correct, the lichens are produced by a symbiosis of fungi and algæ; and possibly this peculiar origin may account for the presence in their tissues of the depside group, which is so conspicuously scarce in the rest of nature.

Among the so-called lichen acids, five have attracted more attention than the rest: orsellinic acid,  $C_8H_8O_4$ ; lecanoric acid,  $C_{16}H_{14}O_7$ ; evernic acid,  $C_{17}H_{16}O_7$ ; gyrophoric acid,  $C_{24}H_{20}O_4$ , and usnic acid,  $C_{18}H_{16}O_7$ . At the time Fischer began his work on these compounds, lecanoric and gyrophoric acid were believed to be built up from two molecules of orsellinic acid, since on careful hydrolysis this acid was obtained from them. Evernic acid was assumed to be some sort of ester-anhydride formed from one molecule of orsellinic acid and one molecule of its methyl ether, evernic acid. Fischer set himself to test these views by synthesis of the compounds, with the results which will be described in the present section.

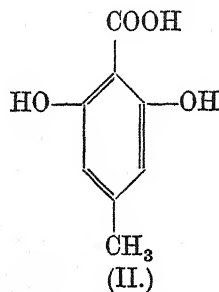
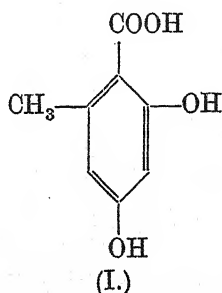
<sup>1</sup> Böttcher, *Ber.*, 1883, 16, 629.

<sup>2</sup> Ransom, *Ber.*, 1898, 31, 1055; 1900, 33, 199.

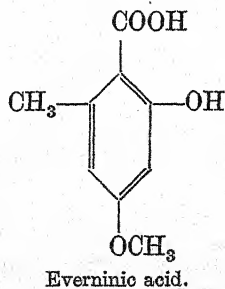
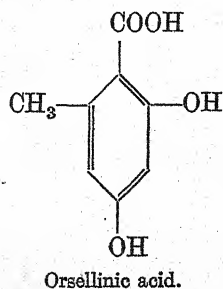
<sup>3</sup> Fischer, Bergmann, and Lipschitz, *Ber.*, 1918, 51, 45; Fischer, *ibid.*, 1915, 48, 271; Fischer and Bergmann, *ibid.*, 1916, 49, 290.

## 2. Orsellinic Acid

In the first place, the structure of orsellinic acid had to be determined. This compound gives a purple-violet tint with ferric chloride and easily decomposes into carbon dioxide and orcinol. The ferric chloride coloration resembles that of salicylic acid; the production of orcinol gives the skeleton of the molecule; so that orsellinic acid appears to be either (I.) or (II.):



Now everninic acid is a methyl ether of orsellinic acid. The structure (I.) permits the existence of two isomeric methyl ethers; whereas since (II.) is a symmetrical molecule, only one methyl ether could be obtained from it. In practice, a second methyl ether, isomeric with everninic acid, has been prepared by acting on orsellinic acid with diazomethane and removing one of the methyl groups from the dimethyl ether thus produced. The existence of this second methyl ether established that orsellinic acid has the asymmetrical formula

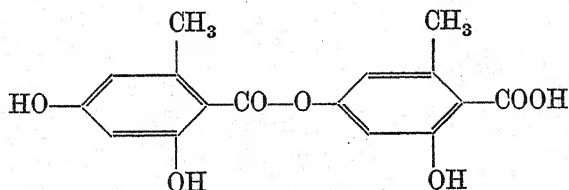


### 3. Everninic Acid

With regard to the structure of everninic acid, Fischer adduced the following evidence in favour of the formula shown above. In the first place, with ferric chloride it gives a strong reddish-violet tint like that of salicylic acid. Secondly, methylation of the phenolic acids with diazomethane takes place more readily in the *para*-position than in the *ortho*-position to the carboxyl group; and the partial methylation of orsellinic acid, when only one hydroxyl is affected, yields everninic acid. Thirdly, similar reasoning suggests that when a carbomethoxy-derivative of orsellinic acid is formed, the carbomethoxy-group occupies the *para*-position. Methylation of the remaining hydroxyl and removal of the carbomethoxy-group leads to the isomer of everninic acid, which is what would be expected.

### 4. Lecanoric Acid

Fischer's next step was to condense dicarbomethoxy-orsellinic acid chloride with orsellinic acid. Since the choice is between condensation in the *ortho*- or the *para*-position, the well-known preference for *para*-condensation leads to the formation of the dideside structure shown below, after removal of the carbomethoxy-groups. On comparing this synthetic substance with natural lecanoric acid, the two were found to be identical, so that the structure of lecanoric acid is :



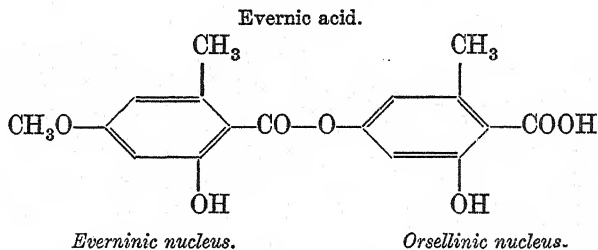
Lecanoric acid.

### 5. Evernic Acid

The problem of the evernic acid constitution may now be considered.

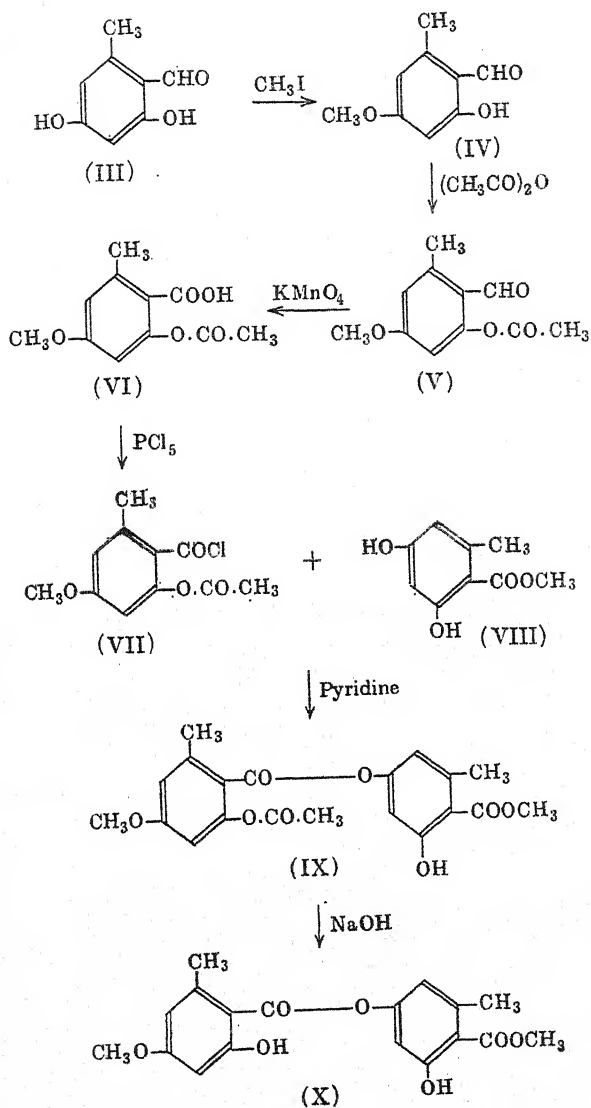
On subjecting lecanoric acid and evernic acid to total methylation, Fischer found that the end-products were identical. Since lecanoric acid is a *para*-compound, this proves that evernic acid also is a *para*-didepside derivative, differing from lecanoric acid only in that it has a methoxy-group instead of one of the hydroxyl radicles of lecanoric acid.

Now the hydrolysis of evernic acid yields orsellinic acid and everninic acid. But, as we have seen earlier in this section everninic acid has no free hydroxyl group in the *para*-position to the carboxyl; for this point is occupied by a methoxy radicle. Since this precludes *para*-coupling with everninic acid acting as a phenol, it is clear that in evernic acid, the acidic part of the molecule must be the everninic nucleus; while the phenolic portion is furnished by orsellinic acid, which has a free hydroxyl radicle in the required *para*-position. The formula for evernic acid must therefore be :



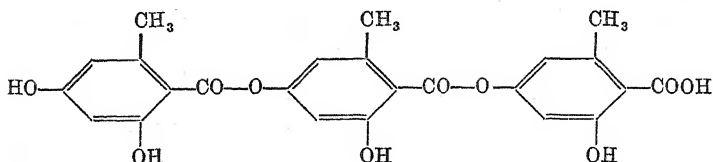
This structure has been confirmed by the synthesis of methyl evernate, which is identical with the methyl ester prepared from the natural acid.<sup>1</sup> By the successive actions of methyl iodide and acetic anhydride or cetyl aldehyde (III.) was converted into acetyleverninaldehyde (V.). This aldehyde was converted into the corresponding acid (VI.) by the action of potassium permanganate solution. The acid chloride (VII.) was prepared in the usual way and on condensation with methyl orsellinate (VIII.) yielded methyl O-acetylevernate (IX.). Hydrolysis of the acetate with dilute sodium hydroxide solution gave methyl evernate (X.). The formulæ will make the steps of the synthesis clearer :—

<sup>1</sup> Robertson and Stephenson, *J.*, 1932, 32, 1388.



## 6. Gyrophoric Acid

Gyrophoric acid is of special interest as it is now known to be one of the small number of natural tridepsides. On hydrolysis it yields orsellinic acid only. Analysis and molecular weight determination pointed to it being a tridepside.<sup>1</sup> These facts led to the inference that the acid has the structure :—

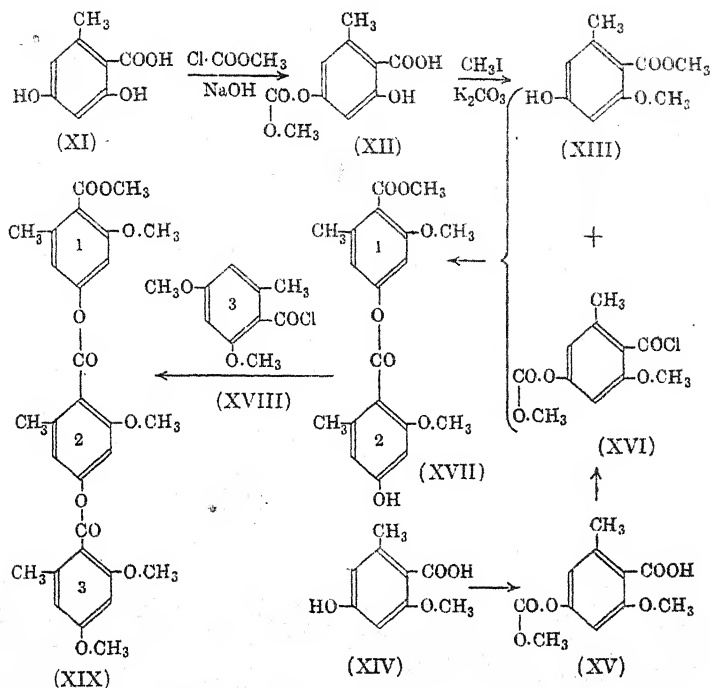


made up of three orsellinic acid residues. This structure has been shown to be correct by the syntheses of methyl tetramethylgyrophorate<sup>2</sup> and methyl tetra-acetylgyrophorate.<sup>3</sup> In each case the synthetic product was identical with the corresponding derivative prepared from the natural substance. The synthesis of methyl tetramethylgyrophorate was carried out using orsellinic acid and *isoevernic* acid as the starting materials of known structures. Orsellinic acid (XI.) may be converted into the *p*-monocarbomethoxy-derivative (XII.) by the action of sodium hydroxide solution and methyl chloro-formate. The para-derivative is formed, as the second hydroxyl group in the orsellinic acid molecule is in the *ortho*-position to the carboxyl group and does not react under the experimental conditions. The action of methyl iodide and potassium carbonate solution produced methyl *isoeverninate* (XIII.). *Isoevernic* acid (XIV.) was converted into its carbomethoxy-derivative (XV) and the acid chloride (XVI.) condensed with methyl *isoeverninate* (XIII.) to yield methyl O-dimethylecanorate (XVII.). This compound was condensed with O-dimethylorsellinoyl chloride (XVIII.) to produce methyl O-tetramethylgyrophorate (XIX.), as follows :—

<sup>1</sup> Asahina and Watanabe, *Ber.*, 1930, 60 [B], 3044.

<sup>2</sup> Asahina and Fuzikawa, *Ber.*, 1932, 65, [B], 983.

<sup>3</sup> Canter, Robertson and Waters, *J.*, 1933, 493.

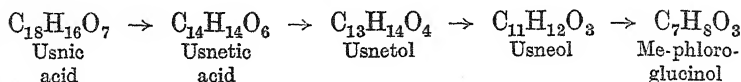


### 7. Usnic Acid

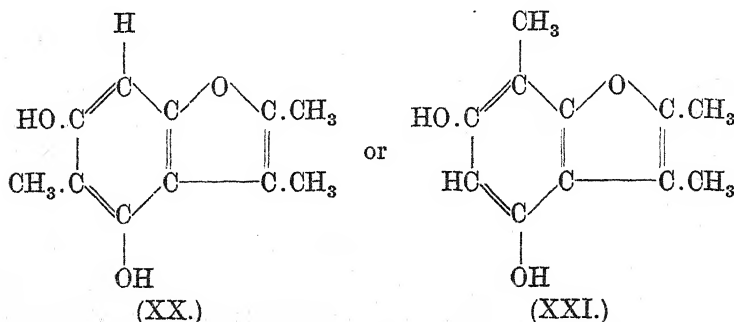
Usnic acid is of widespread occurrence in lichens. Its molecular formula has been established as  $\text{C}_{18}\text{H}_{16}\text{O}_7$ . It is optically active and both the dextro- and lævo-forms have been isolated. It is a comparatively strong acid, liberating acetic acid from sodium acetate. When it is hydrolysed with alkali it breaks down into acetoacetic acid and usnetic acid,  $\text{C}_{14}\text{H}_{14}\text{O}_6$ . By the loss of carbon dioxide usnetic acid is converted into usnetol,  $\text{C}_{13}\text{H}_{14}\text{O}_4$ . This latter substance is phenolic in character and splits off an acetyl group by the action of concentrated alkali yielding the phenol usneol,  $\text{C}_{11}\text{H}_{12}\text{O}_3$ . The successive actions of ozone and sodium hydroxide solution break down usneol to methyl phloroglucinol. An intermediate compound was isolated which was considered to be a methyl phloraceto-



phenone.<sup>1</sup> For reference these degradation products may be shown in the following scheme :



From its relationship to phloroglucinol and phloracetophenone usneol was considered to be a cumarone having the structure (XX.) or (XXI.).



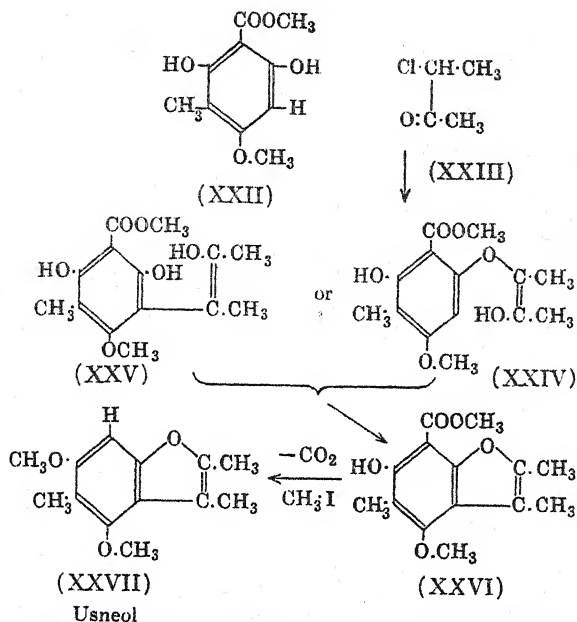
The former structure was shown to be the correct one by the synthesis of usneol dimethyl ether and the comparison made of its properties with those of the dimethyl ether prepared from usneol from natural sources.<sup>2</sup> In this synthesis methyl-2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (XXII.) and 3-chlorobutan-2-one (XXIII.) were condensed by refluxing their acetone solution with potassium carbonate. The cumarone (XXVI.) formed could be produced through either compound (XXIV.) or (XXV.). The cumarone was next decarboxylated and then methylated to yield O-dimethyl usneol (XXVII.). The structures are given on p. 349.

As usnetol splits off an acetyl group under the influence of alkali to give rise to usneol, it was inferred that it had the structure (XXVIII.). This structure was confirmed by the synthesis of O-methylusnetol from 2 : 6-dihydroxy-4-methoxy-3-methyl-acetophenone and 3-chlorobutan-2-one by methods similar to those employed in the synthesis of dimethylusneol.<sup>3</sup>

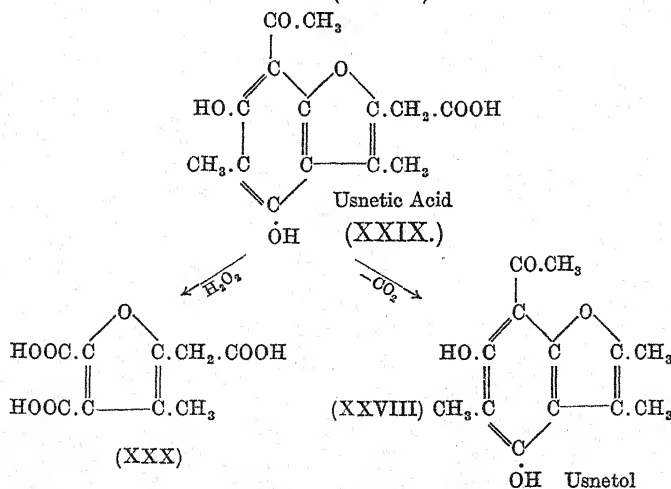
<sup>1</sup> Paterno, *Gazzetta*, 1876, 6, 127; Schoff and Henck, *Annalen*, 1927, 459, 233.

<sup>2</sup> Curd and Robertson, *J.*, 1933, 714.

<sup>3</sup> Curd and Robertson, *J.*, 1933, 1173.

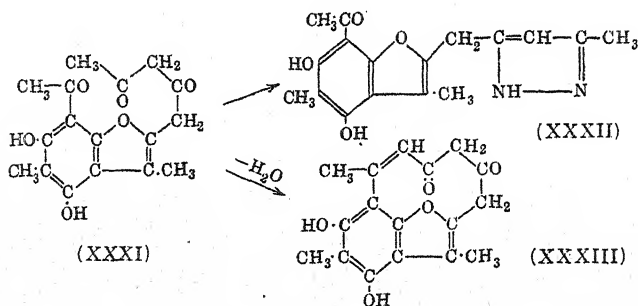


Usnetic acid can be decarboxylated to yield usnetol, and can be oxidized to a tribasic acid derivative of furan. This latter acid was shown to have the structure (XXX.).<sup>1</sup> Consequently usnetic acid has the structure (XXIX.).



<sup>1</sup> Asahina and Yanagita, *Ber.*, 1937, 70, [B], 1500.

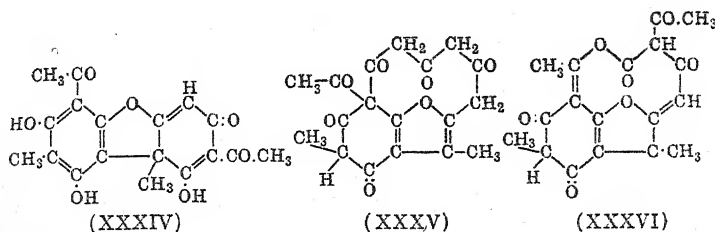
Usnic acid by hydration and loss of carbon dioxide may be converted into decarbousnic acid.<sup>1</sup> As the latter acid can neither be esterified nor decarboxylated, its acidity is attributed to the presence of a 1:3-diketonic group in the molecule. Decarbousnic acid is optically inactive. It reacts with semicarbazide hydrochloride to yield a pyrazole derivative (XXXII), and when treated with aqueous potassium hydroxide breaks down into acetone, acetic acid, usnetic acid and pyrousnic acid. Usnetic acid has been shown to have the structure (XXIX.) and piecing this grouping and one acetone residue together the structure (XXXI.) is obtained for decarbousnic acid.



This structure accounts for the properties of the acid. For example, it contains no asymmetric carbon atom; it contains an acidic enolic group; it permits a suitable explanation to be made of the action of semicarbazide hydrochloride and affords reasonable structures for the products of hydrolysis and dehydration. The pyrazole derivative could have the structure (XXXII.) and decarbousnol obtained by dehydration of the acid would be (XXXIII.).

Structures for usnic acid have, from time to time, been put forward. These provisional structures agree very well with the known properties of the acid, but a choice cannot yet be made between them. Three of these structures, (XXXIV.), (XXXV.) and (XXXVI.), are given for comparison.

<sup>1</sup> Widman, *Annalen*, 1900, 310, 230; 1903, 324, 139; Curd and Robertson, *J.*, 1937, 894.



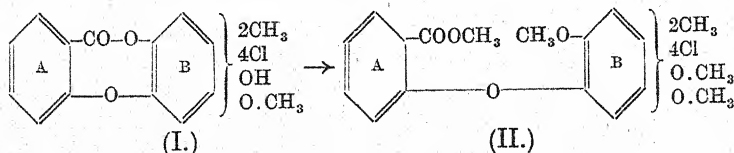
## G.—SOME CHLORODEPSIDES

## 1. General

The lichens *Buellia canescens* and *Lecanora gangaleoides* from various maritime regions yield the depsides diploicin and gangaleoidin respectively. These two substances belong to the very small group of natural organic compounds containing chlorine.

## 2. Diploicin

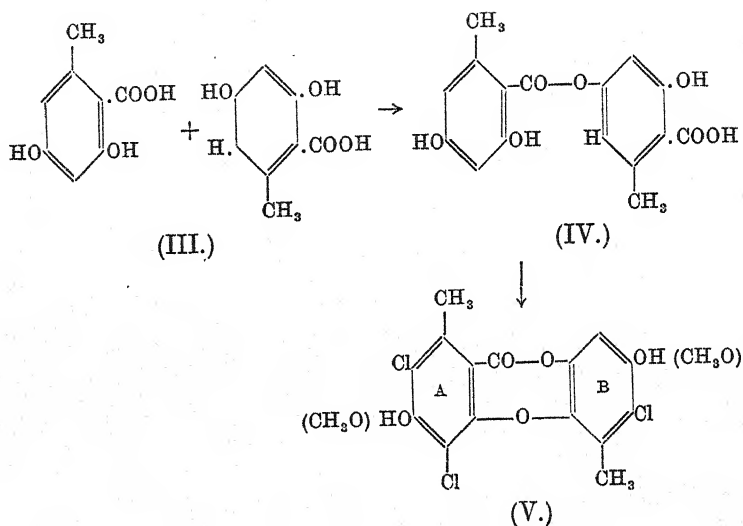
Diploicin has the molecular formula,  $C_{16}H_{10}O_5Cl_4$ .<sup>1</sup> It contains a methoxyl group and one free aromatic hydroxyl group. A lactone grouping is present in the molecule, as it can be hydrolysed to yield a compound which after treatment with diazomethane contains four methoxyl groups (II.). Four of the five oxygen atoms have thus been accounted for. The remaining oxygen atom is chemically inert, and is considered to form an ether link between two aromatic nuclei. As none of the chlorine atoms can be removed by warm alcoholic potash or by boiling acetic anhydride and sodium acetate, they must be directly attached to the benzene nuclei. A Kuhn-Roth  $-C.CH_3$  estimation showed the presence of two  $-C.CH_3$  groups in the diploicin molecule.<sup>2</sup> From these facts the probable partial structure of diploicin is (I.), and the unusual feature presents itself of a



<sup>1</sup> Nolan, *Sci. Proc. Roy. Dublin Soc.*, 1934, 21, 67.

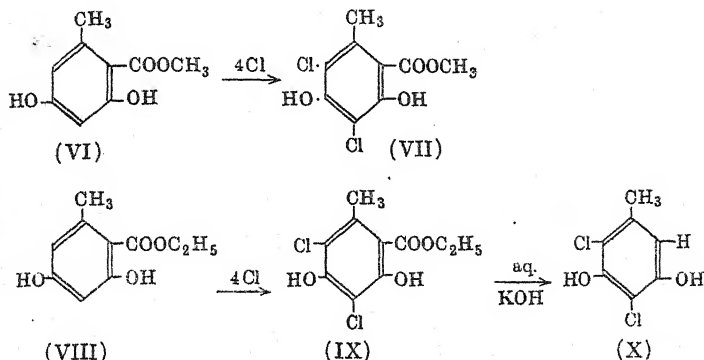
<sup>2</sup> Spillane, Keane, and Nolan, *Sci. Proc. R.D.S.*, 1936, 21, 333.

natural product having all the positions in the benzene nuclei substituted. Inspection of the structures of simpler lichen products points to orsellinic acid (III.) as a possible parent substance of diploicin. The condensation of two molecules of orsellinic acid (III.) with the subsequent elimination of one carboxyl group, followed by chlorination and oxidation could give rise to a compound with the substituents distributed as shown in (V.). These steps may be formulated as follows:—

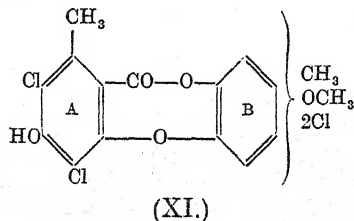


This view of the structure of diploicin is supported by the evidence obtained from the examination of its decomposition products. When diploicin was heated at 270°–275° C. an intermediate compound, C<sub>15</sub>H<sub>8</sub>O<sub>5</sub>Cl<sub>4</sub>, was isolated, which on treatment with warm methyl alcoholic potash in an inert atmosphere yielded 4:6-dichlor-*o*-orsellinic acid methyl ester (VII.); and when diploicin was heated with a mixture of acetic and hydrochloric acids 2:4-dichlor-*o*-resorcinol (X.) was isolated. These two decomposition products were identified by syntheses from *o*-orsellinic acid methyl ester (VI.) and orsellinic acid ethyl ester (VIII.) respectively.<sup>1</sup> The following schemes represent these transformations.

<sup>1</sup> Nolan and Murphy, *Sci. Proc. R.D.S.*, 1940, 22, 315.



These facts leave no doubt about the structure of one half of the diploicin molecule, and accordingly the structure may now be elaborated to (XI).—



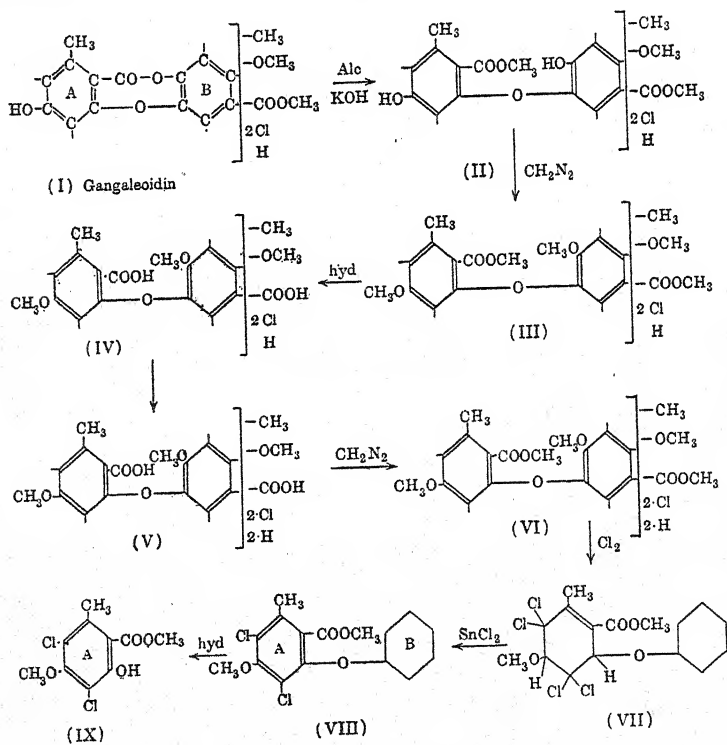
### 3. Gangaleoidin

Gangaleoidin has the molecular formula  $\text{C}_{18}\text{H}_{14}\text{O}_7\text{Cl}_2$ . Analysis showed the presence of two methoxyl groups. There is also present in the molecule one phenolic hydroxyl group. Gangaleoidin (I.) contains one inert oxygen atom, and behaves in the characteristic way of a lactone. When hydrolysed with methyl alcoholic potash it yielded a dicarboxylic ester (II.).<sup>1</sup> Subsequent methylation of this substance with diazomethane gave rise to a product (III.) containing five methoxyl groups. This compound was converted into a trimethoxydicarboxylic acid (IV.) by hydrolysis. One carboxyl group was removed from this acid by the action of hot formic acid.<sup>2</sup> The monocarboxylic acid (V.) formed was then esterified with diazomethane. This fully methylated compound (VI.) was treated

<sup>1</sup> Hardiman, Keane, and Nolan, *Sci. Proc. R.D.S.*, 1935, 21, 141.

<sup>2</sup> Nolan and Keane, *ibid.*, 1940, 22, 199.

with a carbon tetrachloride solution of chlorine and then reduced by means of stannous chloride. Finally hydrolysis with methyl alcoholic potash yielded methyl 4-methoxy-3:5-dichlor-*o*-orsellinate (IX.).<sup>1</sup> From the results obtained by the chlorination of derivatives of *o*-orsellinic acid it may be concluded that a tetrachloro-compound (VII.) was formed, which on reduction was converted into the dichloro-derivative<sup>2</sup> (VIII.). This dichloro-compound then on hydrolysis yielded the orsellinate (IX.). The following partial structures have been assigned to gangaleoidin and the derivatives mentioned.<sup>3</sup>



By similar steps, but using diazoethane instead of diazomethane on gangaleoidin ester (II.), methyl 4-ethoxy-3:5-dichlor-*o*-orsellinate (X.) was obtained. From these results

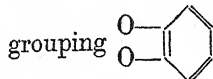
<sup>1</sup> Nolan and Davidson, private communication.

<sup>2</sup> Nolan and Murphy, *Sci. Proc. Roy. Dublin Soc.*, 1940, 22, 315.

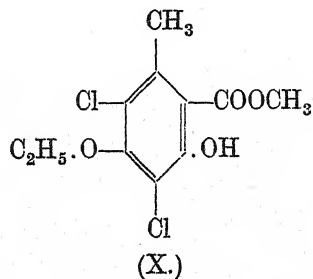
<sup>3</sup> Nolan and Davidson, *ibid.*



some of the substituents of gangaleoidin may be placed with certainty. Firstly, the orsellinate must come from ring A of gangaleoidin as ring B would yield a compound containing the



Secondly, the phenolic hydroxyl of gangaleoidin must be in ring A at position 4 relative to the lactone linkage, as ethylation takes place at this point, and it is most unlikely that demethylation could have taken place in the conversion of gangaleoidin (I.) into its ester (II.). Finally, the remaining two positions in ring A must be occupied either by two chlorine atoms or by one chlorine atom and one hydrogen atom. This being so the remaining substituents  $-\text{CH}_3$ ,  $-\text{O}.\text{CH}_3$ ,  $-\text{COOCH}_3$ , and Cl or H have to be allocated to their positions in ring B. This interesting and difficult work must be left at this stage for further development.



#### H.—THE DEPSIDE TANNIN

By 1913, Fischer's syntheses had resulted in the production of no fewer than twenty-eight dipeptides, two tripeptides, and a pair of tetrapeptides; and from the study of these substances he had gained clear ideas of the general properties of the depside class. To an ordinary investigator, a piece of research on this scale would have been an end in itself; but for Fischer it was a mere preliminary step towards the solution of a greater problem. In his depside researches he was clearing the ground on the road to the real objective which he had set before himself in this branch of chemistry: the elucidation of the constitution of tannin.

The scantiness of our accurate knowledge of tannin at this period has already been indicated in the first section of this chapter. It was not even known with certainty whether glucose did or did not form an integral part of the tannin molecule. Thus at the conclusion of the preliminary work on the depside syntheses, Fischer had to start from the foundation and subject tannin to analysis, in order to settle the question of its main constituents.

First, however, it was necessary to prepare pure samples of tannin, which was done by various methods.<sup>1</sup> Extraction of tannin from an alkaline solution by means of acetic ester proved in the end the most satisfactory process. But even after rigorous purification in this way, the tannin obtained could not be crystallized; so that definite proof of purity was lacking. However, since the same material was obtained from various samples of commercial tannin derived from different sources, it seemed most probable that the purified substance was homogeneous.

It should be noted that this mode of extraction would free the tannin from any substance containing a free carboxyl group; so the possibility of tannin being a glucoside of gallic acid\* is straightway eliminated from consideration.

Fischer's next step was to study the hydrolysis of this most carefully purified tannin, by heating it for seventy hours with 5 per cent. sulphuric acid at 100° C. The results of a large number of tests and control-experiments led him to the conclusion that the tannin molecule on hydrolysis yields ten molecules of gallic acid and one molecule of glucose. No phenolic acid except gallic acid was detected among the hydrolytic products.

At this point, the tannin riddle appeared to be simpler than had been feared. Since glucose contains only five hydroxyl groups, it was evident that it could unite directly with only five acyl radicles. The ten gallic acid nuclei must therefore be so grouped as to present to glucose only five acyl radicles; which is the same thing as saying that some, at least, of them must be joined to one another in depside form. The simplest mode of combination would be to arrange them into five digallic

<sup>1</sup> Fischer and Freudenberg, *Ber.*, 1912, 45, 919; see also Paniker and Strasny, *J.*, 1911, 99, 1819.

\* This is confirmed by Fischer's synthesis of  $\beta$ -glucosido-gallic acid (*Ber.*, 1912, 45, 3773), which was found to be non-identical with tannin.

acid chains; and on Fischer's view, tannin was simply glucose with its five hydroxyl groups esterified by five molecules of digallic acid. Thus at the end of his career, Fischer had come into a field upon which converged two of his earlier lines of research: the investigation of the sugars and the study of the depsides. It seemed a most favourable augury of ultimate success.

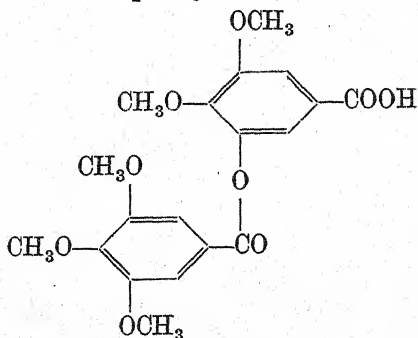
All that was now necessary to strengthen his hypothesis was to prove the presence of digallic acid among the fission products of tannin. But here, strangely enough, only complete failure awaited him. It seems that any agent which breaks the junction between digallic acid and glucose will simultaneously rupture the bond between the two nuclei of digallic acid itself; so that hydrolysis ends in a total disintegration of the complex molecule into its simplest constituents.

Herzig and his collaborators<sup>1</sup> had methylated tannin by means of diazomethane; and on hydrolysis their product yielded trimethyl-gallic acid and the unsymmetrical *meta-para*-dimethyl-gallic acid. This last fact shows that in the tannin molecule *meta*-digallic acid is the esterifier of the glucose hydroxyl radicles.

Since the analytical method had failed to establish the tannin constitution in which he believed, Fischer turned once more to his well-tried weapon of synthesis.

#### I.—THE PENTA-(*m*-DIGALLOYL)-GLUCOSES

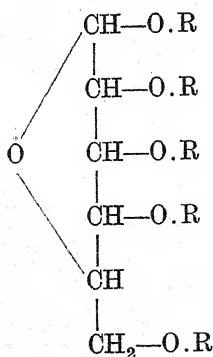
In the field of tannin syntheses, Fischer's first long step was the preparation of a completely methylated *m*-digallic acid:



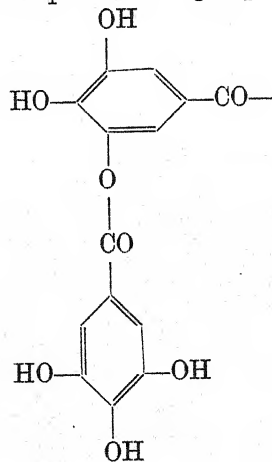
<sup>1</sup> Herzig and others, *Ber.*, 1905, 38, 989; *Monatsh.*, 1909, 30, 543.

which he obtained by acting with trimethyl-galloyl chloride upon the *meta-para*-dimethyl ether of gallic acid. This methylated acid was then used for the complete esterification of the five hydroxyl groups of glucose, producing a substance known as penta-(pentamethyl-*m*-digalloyl)-glucose, two forms of which are known, corresponding to the  $\alpha$ - and  $\beta$ -forms of glucose. This substance was expected to be identical with the compound which is formed when tannin itself is methylated with diazomethane.

It may seem surprising that Fischer did not at once take up the synthesis of the parent substance instead of devoting time to the synthesis of the pentamethyl derivative. The reason lies in the fact that in this case the carbomethoxy method of shielding the hydroxyl radicals had been a failure, since it led to uncrystallizable compounds. But in a short time the acetylation method of protection came to its own in Fischer's laboratory; and by its help he was enabled to prepare the parent penta-(*m*-digalloyl)-glucoses which he surmised might be identical with natural tannin. The structure of these synthetic substances is shown below.

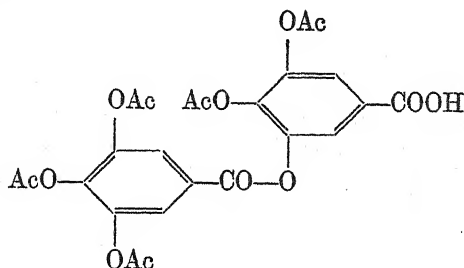


where R represents the group



On paper, at least, this synthesis is simple enough. *Meta*-digallic acid, the synthesis of which has already been described in the sections D and E of this chapter, was completely

acetylated by treatment with acetic anhydride, yielding pent-acetyl-*m*-digallic acid :



This was then converted into the corresponding acyl chloride by treatment with phosphorus pentachloride in presence of chloroform. This acyl chloride in slight excess was mixed with the proper quantity of glucose (either  $\alpha$ - or  $\beta$ -variety) suspended in dry chloroform to which some dry quinoline had been added ; and the mixture was mechanically shaken for two days. After standing for two days more, the mixture was diluted with more chloroform ; the quinoline was removed by means of very dilute sulphuric acid ; the residue was washed with water ; and the chloroform was removed by distillation under reduced pressure.

Final purification was attained by repeatedly dissolving the solid material in chloroform and precipitating it therefrom with methyl alcohol. The ultimate product was a light colourless powder which was easily electrified by rubbing. The yield was surprisingly large for so complex a substance, being 87 per cent. of the theoretical in the case of the  $\alpha$ -glucose derivative, and no less than 95 per cent. of the theoretical yield in the case of the  $\beta$ -derivative. A combustion of the material gave good results ; and an estimation of the acetyl groups was also very close to the theoretical value ; so that there can be no doubt as to the identity of the synthetic product.

The last stage in the synthesis consisted in freeing the compounds from their twenty-five acetyl groups. The acetyl derivatives were dissolved in acetone, cooled to  $0^{\circ}$  C. and then treated with sodium hydroxide solution. A hydrogen atmosphere was employed, to avoid any accidental oxidation by the air. After the completion of the hydrolysis, sulphuric acid was added ; and the penta-[digalloyl]-glucose was extracted by shaking with ethyl acetate. On evaporating off the ethyl

acetate, a syrup was left behind, which eventually solidified to a pale yellow-brown solid. This solid was dissolved in absolute alcohol and an alcoholic solution of potassium acetate was added. The potassium salt was thus precipitated as a thick, almost colourless compound. After further treatment with alcohol, this potassium salt was decomposed with sulphuric acid and the free penta-[digalloyl]-glucose was extracted by means of acetic ester. It proved to be a pale brown, amorphous substance. The yield was 80 per cent. of the theoretical.

A combustion showed good concordance\* between theory and practice; but although chemically the substance was quite pure, it was physically non-homogeneous, since part of it was less soluble in cold water than the remainder. This rather extraordinary state of affairs seems to find its explanation in the semi-colloidal character of the material.

#### J.—PENTA-(*m*-DIGALLOYL)- $\beta$ -GLUCOSE AND CHINESE TANNIN

On collating the properties of his synthetic products and those of certain natural tannins, Fischer detected the closest approximation in the case of Chinese tannin. Since this forms the crux of the whole problem, some space must be devoted to it here; and the chief resemblances between Chinese tannin on the one hand and penta-(*m*-digalloyl)- $\beta$ -glucose on the other must be described in some detail.

(1) The depside derivative and Chinese tannin both show all the normal tannin reactions with gelatine, alkaloid salts, potassium acetate, and arsenic acid. No differences between them were noticeable in any of these respects.

(2) So far as organic solvents go, there is no noticeable difference in the solubilities of the two materials. In aqueous solution, the synthetic product is much less soluble; but this may well be due to a difference in colloidal state between the two substances.

(3) In organic solvents, the optical rotatory powers of the two materials are approximately the same, differing less from each other than the rotatory powers of two samples of a natural

\* It should be noted that with substances of so complex a nature combustion results alone can hardly differentiate between two derivatives which are of nearly the same molecular weight.



tannin derived from the same source. In aqueous solution, the differences are greater; and the synthetic material has a lower rotation than the natural tannin. Here again, however, the colloidal character may be playing a part.

(4) On hydrolysis with dilute sulphuric acid, natural tannin and the synthetic product give like quantities of glucose and gallic acid.

(5) Methylation of both bodies with diazomethane yields very similar products, having very similar optical rotatory power in various solvents.

(6) On acetylation with acetic anhydride and pyridine, both substances are completely acetylated. Estimation of the acetyl radicles in the natural compound gave exactly the same value as in the case of the synthetic material. The optical rotations of the two acetyl-derivatives are close to each other; and neither substance gives a coloration with ferric chloride. On hydrolysis both the natural and the synthetic substances are regenerated intact.

(7) The compositions of corresponding compounds in the two series are identical so far as elementary analysis goes.

From the foregoing, it is self-evident that there is a very close kinship between Fischer's depside derivative and Chinese tannin; and to that extent Fischer's hypothesis as to the nature of tannin is fully justified. If we were to go beyond this, we should be pressing the point further than Fischer himself thought justifiable; for his own conclusion on the subject was couched in the most moderate terms. "On the other hand, there can be no question of a definite identification, since all the materials in question are amorphous and thus lack the surest tokens of homogeneity. Even the synthetic products, as I have repeatedly stated, are not homogeneous, since they are for the most part mixtures of stereoisomers."

#### K.—COMPOUNDS OF HIGH MOLECULAR WEIGHT

One of the by-products of the depside investigations deserves mention here, if only under the guise of a chemical curiosity. Among the natural products there are many compounds of very high molecular weight, such as the proteins and rubber; but our knowledge of their structures is only sketchy, and even



their molecular weights are not known with exactitude. In most cases the colloidal character of the material hinders any accurate molecular weight determination; and inferences can be drawn only from the percentages of certain elements in the compounds. Thus, for example, by making assumptions as to the number of iron atoms in the molecule of oxyhæmoglobin, it is possible from the composition of the compound to make a guess that its molecular weight lies in the neighbourhood of 16,000; but even this is hardly more than a random shot.

It will be remembered that in the course of his work, on the polypeptides, Fischer synthesized the octadecapeptide, *l*-leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine, which has the formula  $C_{48}H_{81}O_{19}N_{18}$  and a molecular weight of 1213. Now in the depside series it is possible to reach much higher stages, if the depside radicles be coupled with sugar nuclei as in Fischer's attempted synthesis of tannin; and in such cases the constitution of the final product is established by the steps in the synthetic process. Fischer thought it worth while to produce one or two of these extremely complex materials.

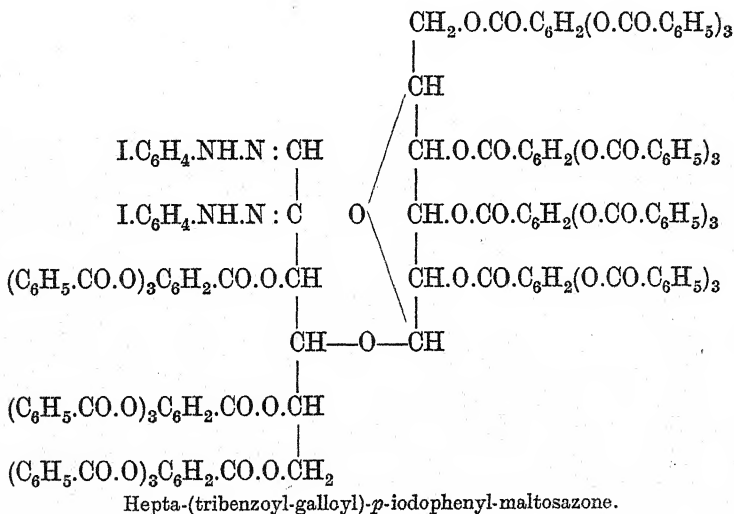
For this purpose, he chose as his basic reagent tribenzoyl-gallic acid,  $(C_6H_5.CO.O)_3C_6H_2.COOH$ , since this substance has the double advantage of being readily obtainable in quantity and yielding a crystalline, easily-purifiable chloride. Its molecular weight, 482, is already a high one; so that by esterifying the acid with a sugar, a very massive molecule can be obtained.

Mannitol was the first sugar chosen for this purpose; and the neutral ester obtained from it had a molecular weight of 2967. Compounds of this type, however, presented the difficulty that the combustion results did not serve to differentiate sharply enough between a fully acylated derivative and one containing fewer acyl radicles; so that a definite proof of the constitution of the materials was lacking; and as the substances are amorphous, no indisputable proof of homogeneity could be adduced.

To get round this, Fischer hit upon the idea of introducing into the molecule a definite number of halogen atoms, so that a halogen estimation would reveal the proportion of the halogen to the remainder of the structure and thus yield a gauge of the number of acyl groups present. This method was tested by esterifying the glucoside of tribromophenol with tribenzoyl-

gallic acid, whereby tetra-(tribenzoyl-galloyl)-tribromophenol-glucoside was formed. From a bromine estimation, the number of tribenzoyl-galloyl groups in the molecule could be determined; and the molecular weight was thus found to be 2349.

Fischer's final attack on the subject yielded a still more striking result. Maltose was treated with *p*-iodo-phenylhydrazine and *p*-iodo-phenyl-maltosazone was produced. This was coupled with tribenzoyl-galloyl chloride in presence of quinine; and the result was a hepta-(tribenzoyl-galloyl)-*p*-iodo-phenyl-maltosazone. The number of acyl radicles in the molecule was determined by an estimation of the iodine percentage, which gave such sharp results that no doubt was left to the homogeneity of the material. The formula of this new gigantic molecule can be represented thus:



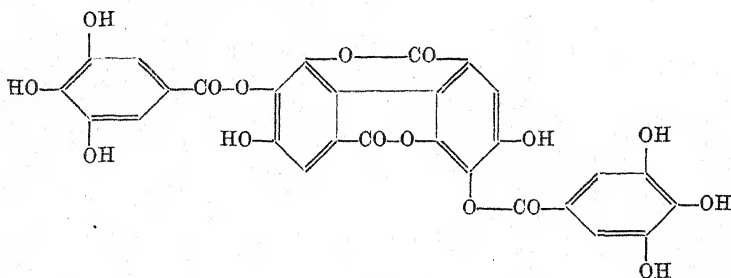
This formula corresponds to  $\text{C}_{220}\text{H}_{142}\text{O}_{58}\text{N}_4\text{I}_2$ , and the compound has a molecular weight of 4021. It is over three times as heavy as Fischer's most complex polypeptide and is by far the most massive molecule yet synthesized with a known structure.

The compound is an amorphous, clear-yellow powder, very slightly soluble in alcohol and ligroin, easily soluble in acetone, chloroform, and benzene. It begins to decompose at about  $145^\circ \text{C}$ ., and at  $160^\circ \text{C}$ . it is converted into a red liquid. An

attempt was made to determine its molecular weight cryoscopically, with bromoform as a solvent; but great difficulty was found in removing the last traces of the solvents with which the material had been purified, since these were hard to drive out of the amorphous body. The molecular weight results gave an average of 3503 instead of 4021. When the experimental difficulties of purification are taken into account, this seems a very good result, and it certainly shows that the freezing-point method is not completely at fault even in extreme cases like this, since it at least enables us to say that the substance is monomolecular.

#### L.—THE ELLAGITANNINS

These are related to the depside tannins and yield ellagic acid on hydrolysis. Very little is known about the structures of this type of tannin. One hypothesis is that it is a galloyl derivative of ellagic acid of the type shown (I).<sup>1</sup>



(I.)

This view is supported by the fact that a synthetic tetra-galloyl ellagic acid had properties closely resembling those of ellagitannin.<sup>2</sup> Ellagic acid itself is an interesting compound and is related to both the normal depsides and the  $\alpha$ -pyrones. It has the molecular formula  $C_{14}H_6O_8$  and forms a tetramethyl ether, indicating the presence of four free hydroxyl groups in the molecule. On being boiled with potassium hydroxide it yields pentahydroxydiphenyl-methylolid (III).<sup>3</sup> On fusion with alkali the product is hexahydroxydiphenyl (IV).<sup>4</sup> When the

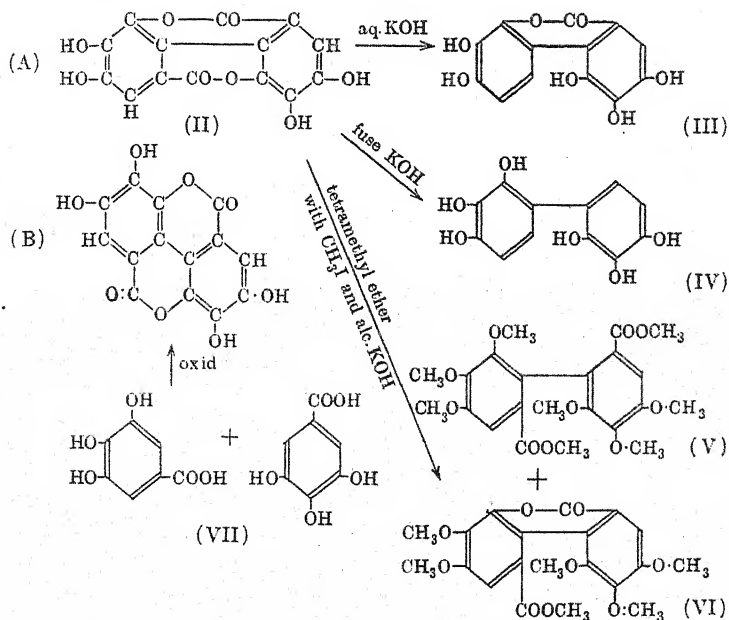
<sup>1</sup> Perkin and Nierenstein, *J.*, 1905, 87, 1427.

<sup>2</sup> Nierenstein, *Ber.*, 1911, 44, 837.

<sup>3</sup> Perkin and Nierenstein, *loc. cit.*

<sup>4</sup> Barth and Goldschmidt, *Ber.*, 1879, 12, 1242.

tetramethyl ether of ellagic acid is treated with methyl iodide and alcoholic potash it is converted into diphenyl 3:4:5:8:9:10-hexamethoxy-1:6-dicarboxylic methyl (V.) and diphenyl-methylolid-3:4:5:8:9-pentamethoxy-6-carboxylic methyl ester (VI.).<sup>1</sup> Ellagic acid may readily be prepared from gallic acid (VII.) by oxidation. Taking the known facts into consideration the most suitable structure for ellagic acid is (II.). This has been written in two ways, (A) and (B), to bring out the connection with the normal depsides on the one hand and on the other to show the relationship to the  $\alpha$ -pyrones.



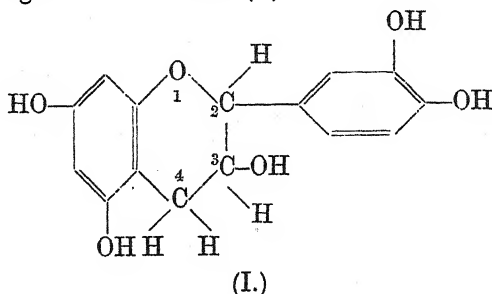
## M.—THE PHLOBATANNINS

### 1. Introductory

These substances come under the heading of non-hydrolysable tannins, very little is known about the structures of many of them. The catechol tannins have received the most attention. Catechins have been isolated from a large variety of plants,

<sup>1</sup> Herzig and Pollak, *Monatsh.*, 1908, 29, 263.

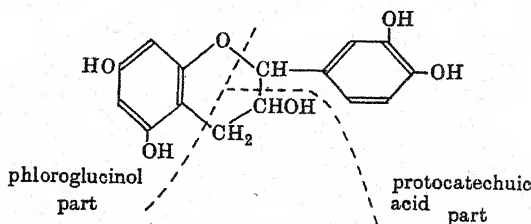
particularly from the bark of trees. Catechin itself is not a tannin, but is presumably a degradation product of tannins. It has been given the structure (I.).



Inspection of this formula shows that it contains two asymmetric carbon atoms, (2) and (3), in the heterocyclic ring. In addition to optical activity there is the possibility of *cis*- and *trans*-isomerism due to different arrangements of the groups and atoms attached to these two carbon atoms. Further, if natural substances exist in which the hydroxyl group and the side-chain catechol nucleus occupy other positions in the heterocyclic ring, it is evident that a large number of isomers of different types may exist and that great caution is necessary in interpreting experimental results.

## 2. The Structures of the Catechins

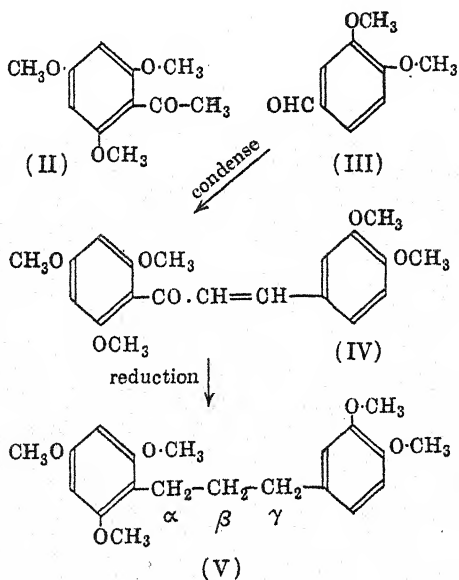
On fusion with alkali catechin decomposes with the production of protocatechuic acid and phloroglucinol,



Catechin forms penta-acetyl and penta-benzoyl derivatives, a tetramethyl ether and an acetyltetramethyl ether, and with some difficulty a pentamethyl ether.<sup>1</sup> When the tetramethyl

<sup>1</sup> von Kostanecki et al., *Ber.*, 1902, 35, 1867, 2410; 1903, 39, 4007; 1907, 40, 4910.

ether was oxidized with potassium permanganate it yielded veratric acid as one of the products.<sup>1</sup> The penta-acetyl derivative when heated with an alcoholic solution of potassium acetate lost four of its acetyl groups. These facts point to one of the five hydroxyl groups being alcoholic in type. When catechin tetramethyl ether was reduced with sodium and alcohol and then methylated with methyl sulphate a compound was formed, which was shown by its synthesis to be 2:4:6:3':4'-penta-methoxy- $\alpha\gamma$ -diphenylpropane.<sup>2</sup> This synthesis was carried out as follows, phloracetophenone (II.) and veratraldehyde (III.) were condensed with the formation of 2:4:6-trimethoxyphenyl-3':4'-dimethoxystyryl ketone (IV.). The unsaturated ketone on reduction yielded 2:4:6:3':4'-pentamethoxy- $\alpha\gamma$ -diphenylpropane (V.).



Cyanidin chloride (VI.) has been reduced by means of platinum and hydrogen to yield *r*-epicatechin (VII.), which can be isomerized to *r*-catechin.<sup>3</sup> Similarly cyanidin pentamethyl ether

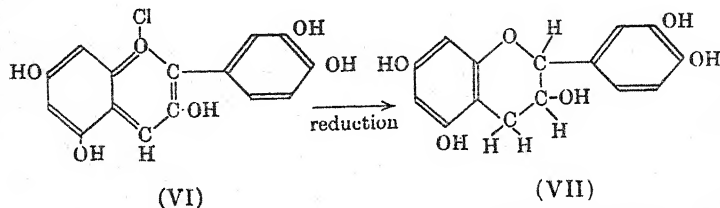
<sup>1</sup> Perkin and Yoshitake, *J.*, 1902, 81, 1162; 1905, 87, 398.

<sup>2</sup> Freudenberg, *Ber.*, 1920, 53, 1416.

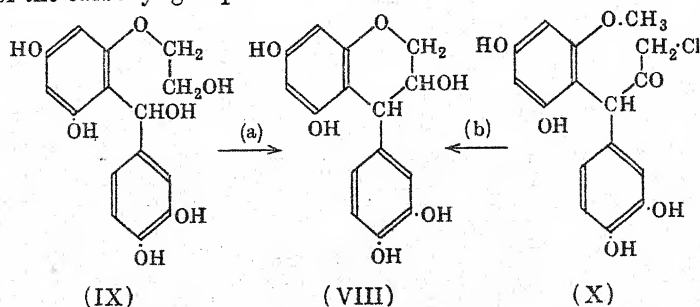
<sup>3</sup> Freudenberg, Fikentscher, Harder, and Schmidt, *Annalen*, 1925, 444, 134.



can be reduced to pentamethyl-*r*-catechin, and fisetinidin chloride yields quebracho catechin.<sup>1</sup> The reduction of cyanadin chloride may be formulated as,



The identification of the reduction product of methylated catechin as an  $\alpha$ - $\gamma$ -diphenylpropane derivative, and the transformation of cyanidin chloride into catechin leave very little doubt about the structure of catechin. The following isomers have been isolated, catechin from gambier catechu yields *d*-, *l*- and *r*-catechins; acacia heart-wood yields *l*-epicatechin and a small amount of *r*-catechin and pegu catechin yields *l*- and *r*-epicatechin. *d*-Epicatechin has been isolated by the isomerization of *d*-catechin.<sup>2</sup> In opposition to these views of the structures of the catechins it has been claimed that the catechin from acacia heart-wood is not a stereoisomer but a position isomer, acacatechin of the structure (VIII.), and in support of this two syntheses have been given, (a) from *l*-leucomaclurin-glycol ether (IX.), and (b) by ring closure of the compound (X.) followed by reduction of the carbonyl group.<sup>3</sup>



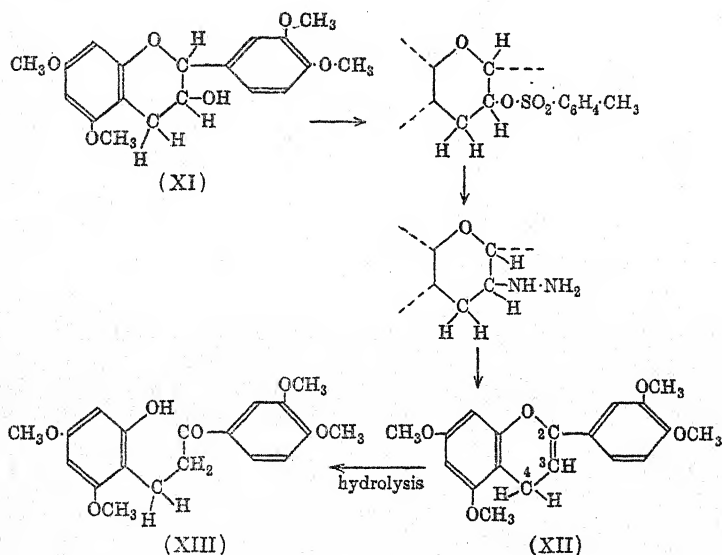
<sup>1</sup> Freudenberg and Maitland, *J. Soc. Leather Trades Chem.*, 1934, 18, 156.

<sup>2</sup> Freudenberg et al., *Ber.*, 1921, 54, 1204; 1922, 55, 1734; *Annalen*, 1924, 437, 274.

<sup>3</sup> Nierenstein, *Annalen*, 1913, 396, 194; *J.*, 1920, 971, 1151; 1921, 164; 1922, 601; *Ber.*, 1922, 55, 3831; *J. Amer. Chem. Soc.*, 1926, 84, 1964; 1930, 52, 1672.



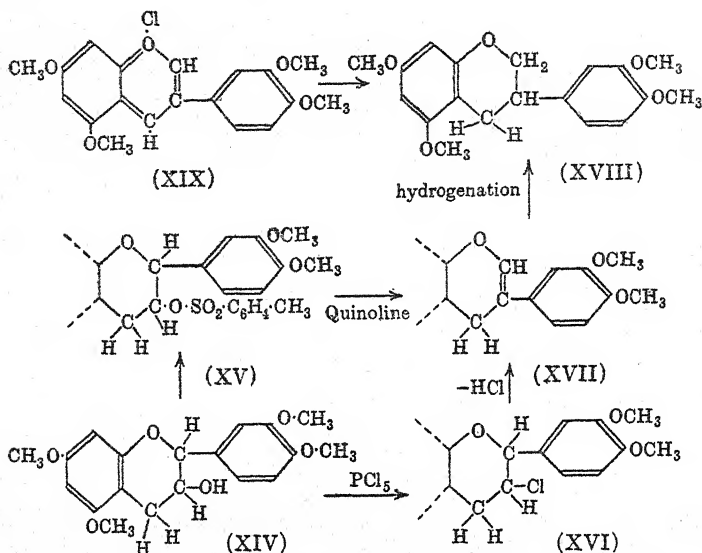
It has been found that the hydrazine derivative of tetramethyl-*d*-catechin formed through its toluene sulphonic ester is very hard to dehydrate. On the other hand by the same treatment tetramethyl-*epi*-catechin (XI.) readily yields its dehydration product, tetramethylanhydro-*epi*-catechin (XII.). For these reasons catechin is regarded as the *trans*-compound and *epi*-catechin as the *cis*-form.<sup>1</sup> The steps in the dehydration have been formulated as follows :—



The anhydro-compound (XII.) in acetic acid solution adds on one molecule of water and is converted into the chalcone derivative (XIII.) of known structure. The fact that tetramethylanhydro-*epi*-catechin (XII.) is optically inactive eliminates the possibility of a double bond being between carbon atoms (3) and (4), and consequently rules out position (4) for the hydroxyl group in the original catechin (XI.). A position isomer (XVII.) of tetramethylanhydro-*d*-catechin has been isolated by heating the catechin sulphonic ester (XV.) for a considerable time with quinoline. This same compound was obtained by converting tetramethylcatechin (XIV.) into its chloride (XVI) and then

<sup>1</sup> Freudenberg et al., *Annalen*, 1924, 436, 286; 1925, 441, 309.

removing one molecule of hydrogen chloride by the action of pyridine.<sup>1</sup> These changes are formulated below.



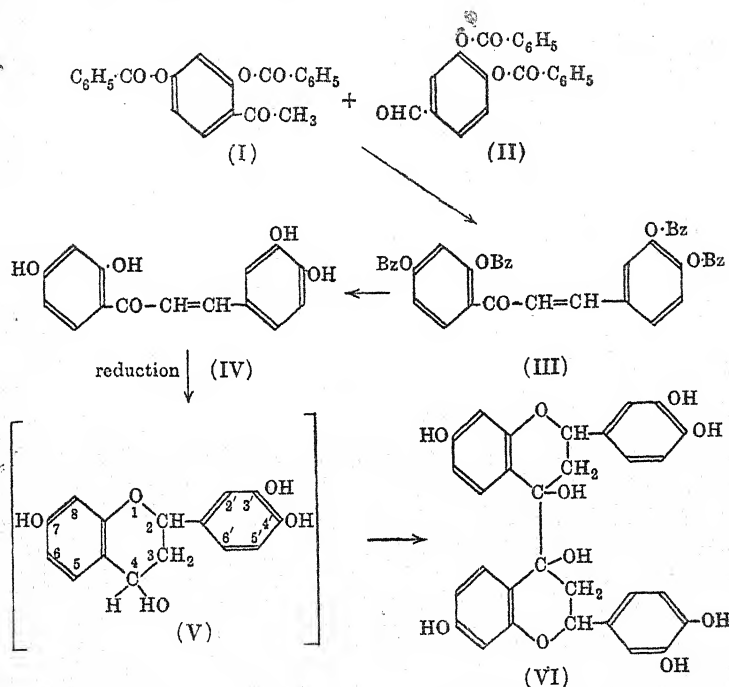
The wandering of the veratryl group has been confirmed by the synthesis of the hydrogenation product through the oxonium chloride (XIX.). This chloride on reduction with platinum black afforded 3-(3':4'-dimethoxyphenyl)-5:7-dimethoxychroman (XVIII.) identical with the hydrogenation product obtained from the methylated natural catechin.

### 3. The 4-Hydroxy Flavans and Flavpinacols

Turning now to another aspect of the problem of the structure of the phlobatannins, the 4-hydroxy flavans are of interest on account of the relationship between them and certain natural phlobatannins. When the resorcinol derivative, resacetophenone dibenzoate (I.), was condensed with protocatechualdehyde dibenzoate (II.) by means of hydrogen chloride in ethylacetate, 2:4:3':4'-tetrabenzoyloxychalkone (III.) was formed. The corresponding hydroxy compound, 2:4:3':4'-tetrahydroxychalkone (IV.) was isolated on debenzoylation. Reduction of

<sup>1</sup> Drumm, Macmahon, and Ryan, *Proc. Roy. Irish Acad.*, 1923, **39B**, 41; 1924, 149.

the tetrahydroxy compound (IV.) with zinc dust gave the *bis*-compound (VI.). By measuring the amount of hydrogen absorbed during the reduction of the chalkone it was concluded that the *bis*-compound was formed and not the simpler flavan (V.).<sup>1</sup> The steps are formulated below.



By the same methods *bis*-(5:7:3':4'-tetrahydroxy) flavpinacol and the 7:8:3':4'-tetrahydroxy compound were prepared. All these compounds bear a close resemblance to the natural hemlock phlobatannin. An exhaustive comparison of the colour and precipitation reactions of hemlock tannin with those of the synthetic flavpinacols showed striking resemblances between the two groups. Similarly the absorption spectra of the two groups are practically identical.<sup>2</sup> There can be no doubt that hemlock tannin is closely related to these flavpinacols.

<sup>1</sup> Russell, J., 1934, 218; Russell and Todd, *ibid.*, 1066, 1506.

<sup>2</sup> Russell, Todd, and Wilson, J., 1934, 1940.

## CHAPTER XII

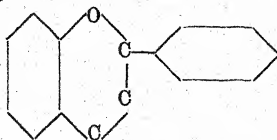
### THE LIGNANS

#### 1. Introductory

THESE compounds occur principally in natural resins and in the wood of the Coniferae. They have also been obtained from the seeds, roots and leaves of various other plants. The lignans

contain the skeleton  $\text{C}_6-\text{C}-\overset{\text{C}}{\overset{\text{C}}{\text{C}}}-\text{C}-\text{C}_6$ , and are phenolic in character. Structurally they may be regarded as derived from two molecules of coniferyl alcohol (I.). The aromatic portions of the molecule are in most cases derived from guaiacol. The simpler members of the group, such as *l*-guaiaretic acid (II.) and *l*-matairesinol (III.) are open-chain aryl compounds. In some cases they are tetralin derivatives due to cyclic condensation of the aliphatic part of the molecule. Examples of this type are *l*-podophyllotoxin (IV.) and *l*-conidendrin (V.). The lignans have been conveniently classified as, (a) diarylbutanes (II.) and (III.), (b) tetrahydronaphthalenes (IV.) and (V.), and (c) tetrahydrofurans (VI.) and (VII.).<sup>1</sup>

It is an interesting fact that the lignans form part of the large group of natural compounds containing the structural unit  $\text{C}_6-\text{C}_3$ .<sup>2</sup> It is assumed that glucose is the parent natural material and that its fission accounts for the  $\text{C}_3$  unit.<sup>3</sup> Tyrosine, cinnamic acid and its numerous relatives, such as coniferyl alcohol and coumarin are simple examples of this association of  $\text{C}_6$  and  $\text{C}_3$  units. The more complex molecular groupings of the flavones and the related anthocyanidins and catechins contain the grouping  $\text{C}_6-\text{C}_3$  with another hexose unit attached normally to the triose unit,



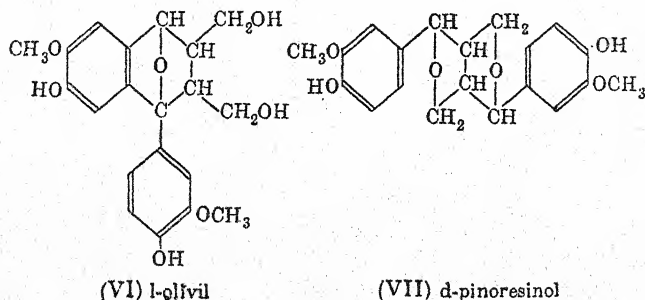
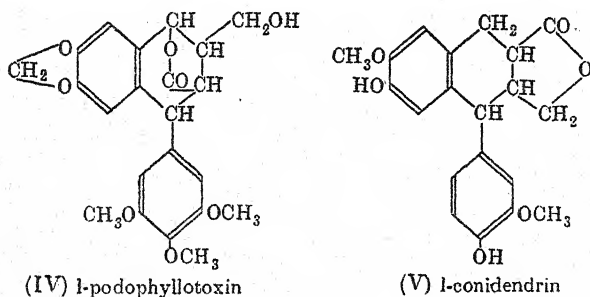
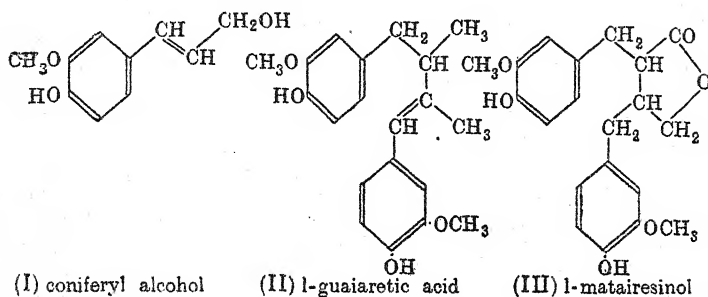
<sup>1</sup> Haworth, *Nature*, 1941, 147, 255.

<sup>2</sup> Haworth, *loc. cit.*

<sup>3</sup> Robinson, *Proc. Univ. Durham Phil. Soc.*, 1927-28, 8, 14.

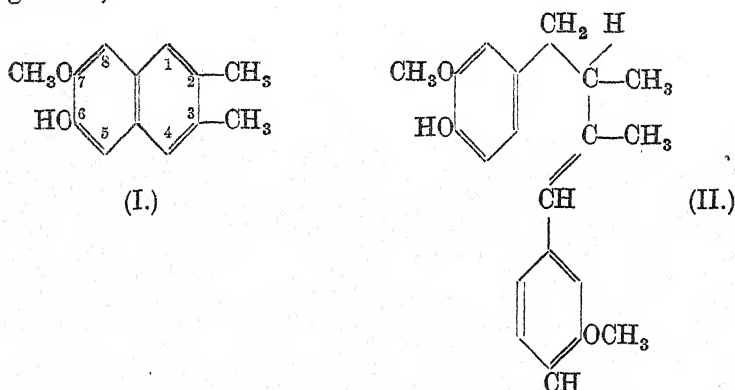
Inspection of the structures assigned to the lignans shows that these molecules are made up of two  $C_6-C_3$  groups linked together through  $\beta$ -carbon atoms of the triose parts.

A large number of lignans have been isolated and their structures made clear. Three typical compounds will be dealt with here to give an insight into the methods employed in the determination of constitutions in this group of resin acids.



## 2. Guaiaretic Acid

Guaiaretic acid,  $C_{20}H_{24}O_4$ , is a constituent of guaiacum resin obtained from the heartwood of *Guaiacum officinale* or of *G. sanctum*. It is optically active, showing a lævo-rotation of  $94^\circ [\alpha]_D$ . The acid yields a diacetate and a dibenzoate, and when treated with methyl sulphate and hot aqueous-alcoholic potassium hydroxide it is converted into a derivative containing four methoxy groups,  $C_{18}H_{16}(OCH_3)_4$ . This points to the presence of two hydroxyl and two methoxyl groups in the molecule. On reduction guaiaretic acid and its tetramethoxy-derivative both yield dihydro-compounds. There is, therefore, an ethylenic linkage in the molecule. Guaiaretic acid when heated yields 2:3-dimethyl-6-hydroxy-7-methoxynaphthalene (I.)<sup>1</sup> (pyroguaiacin).



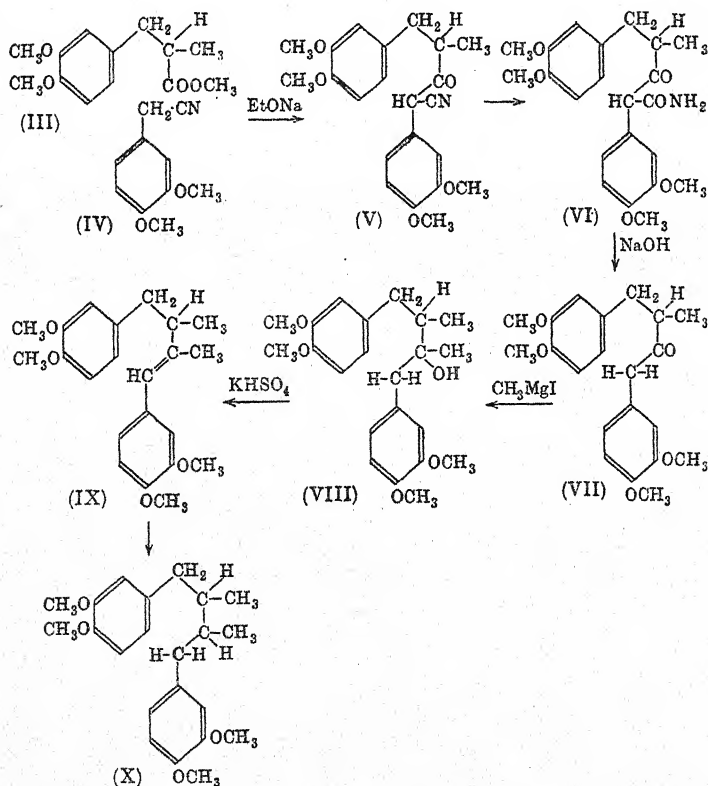
Dihydroguaiaretic acid obtained from guaiaretic acid is a mixture of optically active and inactive compounds. The inactive compound is thought to arise from internal compensation due to the formation of a second asymmetric carbon atom as a result of the reduction. Taking all these facts into consideration a possible structure for guaiaretic acid is (II.). This has been confirmed by the synthesis of *dl*-dihydroguaiaretic acid dimethyl ether (IX.) in the following way. Methyl  $\beta$ -3:4-dimethoxyphenyl- $\alpha$ -methylpropionate (III.) and 3:4-dimethoxyphenyl-acetonitrile (IV.) in benzene solution were condensed by means of potassium ethoxide and yielded the cyano-ketone (V.). This

<sup>1</sup> Schroeter, Lichtenstadt and Irineu, *Ber.*, 1918, 51, 1537; Haworth and Mavin, *J.*, 1932, 1485.



substance on hydrolysis was converted into  $\beta$ -keto- $\alpha\delta$ -bis-3:4-dimethoxyphenyl- $\gamma$ -methylvaleramide (VI.). Alkaline hydrolysis eliminated the amido group from this compound with the formation of the ketone (VII.). The action of methyl magnesium iodide converted the ketone into the corresponding carbinol (VIII.), which on dehydration with potassium hydrogen sulphate yielded *dl*-guaiaretic acid dimethyl ether (IX.). The guaiaretic acid was reduced by hydrogen in the presence of palladised charcoal to *dl*-dehydroguaiaretic acid dimethyl ether (X.) identical with the corresponding compound prepared from natural guaiaretic acid.<sup>1</sup>

The structural steps are as follows :—

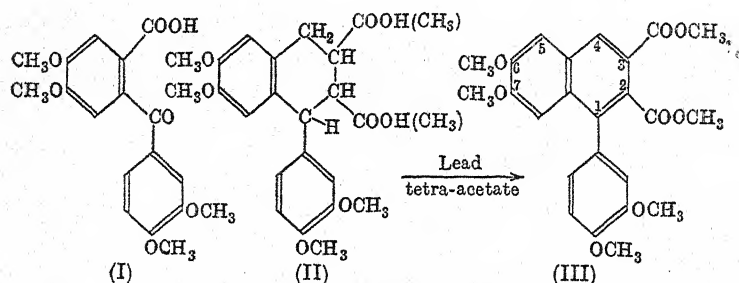


<sup>1</sup> Haworth, Mavin, and Sheldrick, *J.*, 1934, 1423.



## 3. Conidendrin (Tsugaresinol)

Conidendrin was first isolated from waste sulphite liquors, and later from the wood resin of Japanese hemlock and European spruce.<sup>1</sup> It has the molecular formula  $C_{20}H_{20}O_6$ . It forms a diacetate, yields a hydroxy-acid,  $C_{20}H_{22}O_7$ , and can be converted into a tetramethoxy compound by the action of methyl sulphate. Conidendrin, therefore, appears to be a diphenolic dimethoxy lactone.<sup>2</sup> When the tetramethoxy compound was oxidized with potassium permanganate one of the products was 4:5:3':4'-tetramethoxy-2-benzoylbenzoic acid (I.); when the oxidizing medium was alkaline sodium hypobromite, in addition to the benzoylbenzoic acid derivative, a dibasic acid,  $C_{22}H_{24}O_8$  (II.) was isolated. The dimethyl ester of this acid when dehydrogenated by the action of lead tetra-acetate was converted into methyl 6:7-dimethoxy-1-(3':4'-dimethoxyphenyl) naphthalene-2:3-dicarboxylate (III.).<sup>3</sup>



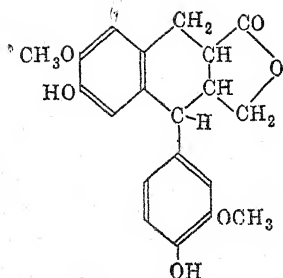
Bearing in mind the fact that the dibasic acid (II.) was obtained from methylated conidendrin by oxidation two possible structures for conidendrin are (IV.) and (V.), the phenolic hydroxyl groups being placed at the positions shown from the relationship with other natural compounds.

The positions of the hydroxyl groups were established by ethylating conidendrin and then oxidizing the product with

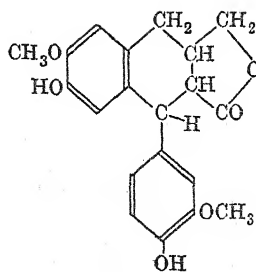
<sup>1</sup> Lindsay and Tollens, *Annalen*, 1892, 267, 353; Kawamura, *Bull. Imp. Forestry Exp. Stat. Tokyo*, 1932, 31, 73.

<sup>2</sup> Holmberg, *Svensk Kemisk Tidskrift*, 1920, 32, 56; *Ber.*, 1921, 54 [B] 2389; Holmberg and Sjöberg, *ibid.*, 2406.

<sup>3</sup> Erdtman, *Annalen*, 1934, 513, 229.

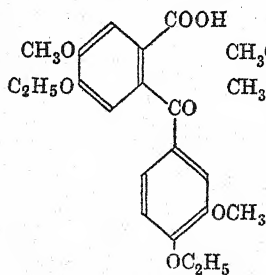


(IV.) Conidendrin

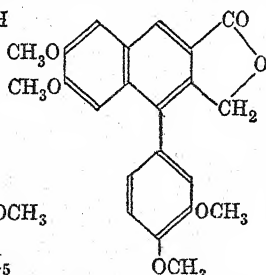


(V.)

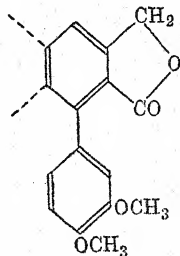
permanganate. The compound isolated was 5-methoxy-4-ethoxy-2-(3'-methoxy-4'-ethoxybenzoyl) benzoic acid (VI.). The production of this substance leaves no doubt about the positions of the free phenolic groups in conidendrin.<sup>1</sup> Turning now to the exact arrangement of the lactone ring. When natural conidendrin was methylated and then dehydrogenated by means of lead tetra-acetate a lactone,  $C_{22}H_{20}O_6$  was isolated. This compound was the naphthalene derivative (VII a.) or (VII b.) with the lactone ring of conidendrin intact.



(VI)



(VIIa)



(VIIb)

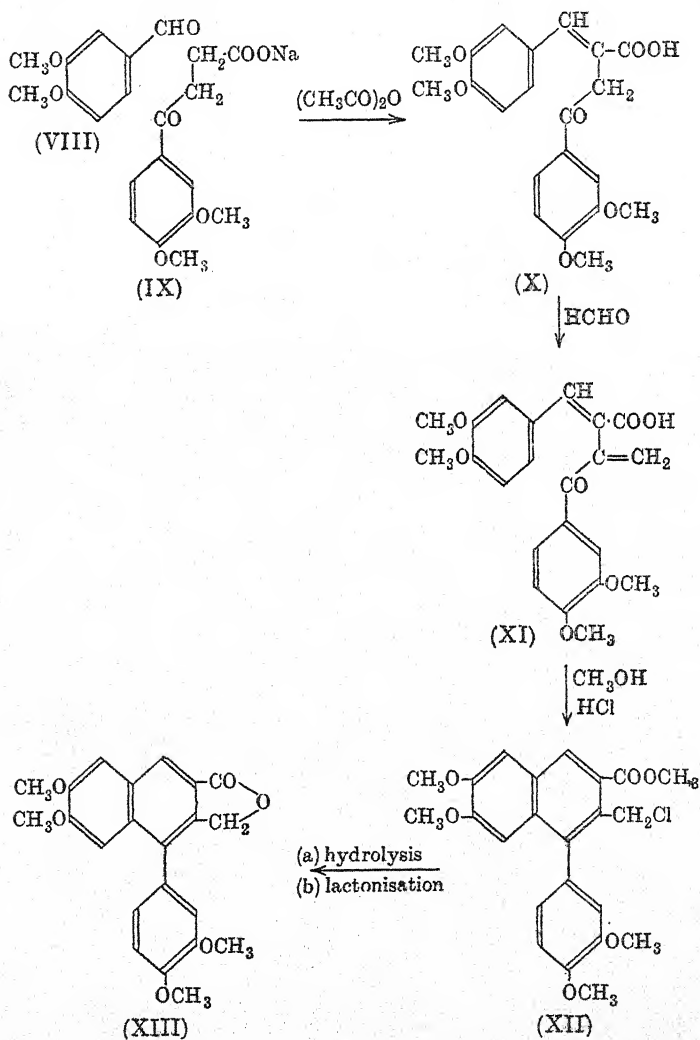
On this assumption the two naphthalene derivatives corresponding to structures (VII a.) and (VII b.) were synthesized by unequivocal steps, and that of type (a) was shown to be identical with the lactone derived from conidendrin.<sup>2</sup> The synthetic lactone (VII a.) was prepared in the following way. Veratraldehyde (VIII.) and sodium  $\beta$ -(3 : 4-dimethoxybenzoyl) propionate (IX.) were condensed by means of acetic anhydride to give a lactone, which was hydrolysed to the free acid (X.). This acid

<sup>1</sup> Haworth and Sheldrick, *J.*, 1935, 636.

<sup>2</sup> Haworth, Richardson, and Sheldrick, *J.*, 1935, 1576.

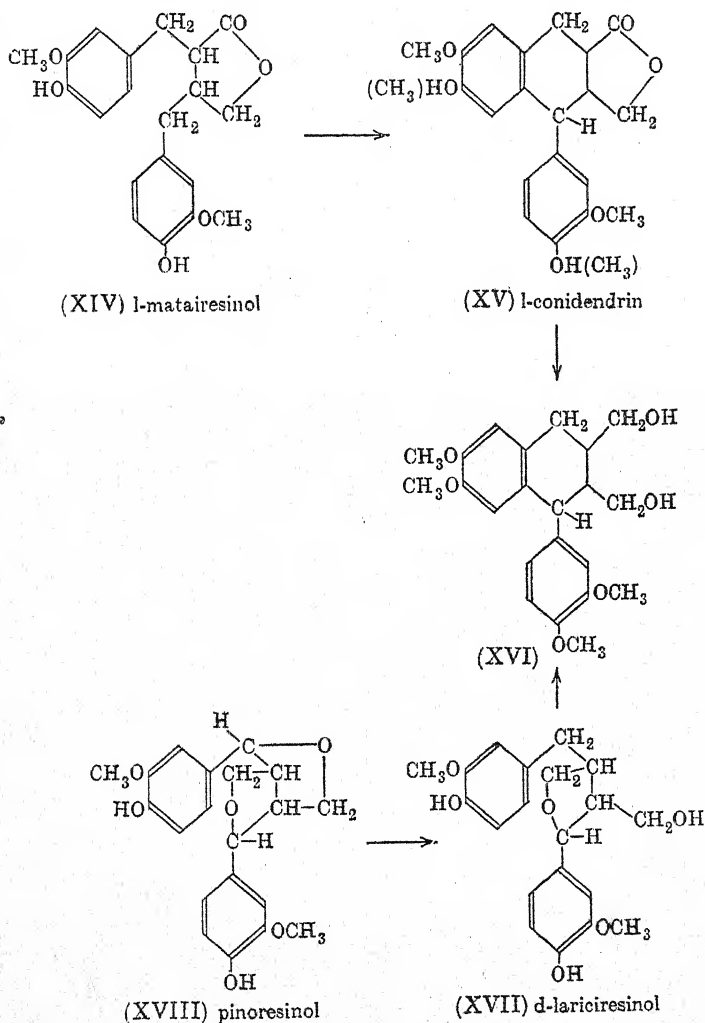
with formaldehyde in cold alkaline solution gave a quantitative yield of the benzylidene derivative (XI.).

The action of warm methyl alcoholic hydrogen chloride on the benzylidene derivative resulted in cyclisation and chlorination. The product isolated was the methyl ester (XII.). Finally, alkaline hydrolysis followed by lactonisation of the naphthalene



derivative yielded the lactone of 6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid (XIII).<sup>1</sup> Consequently structure (IV.) must be given to conidendrin.

The close structural relationship of conidendrin to lignans of the other two types is shown by the ready interconversions which

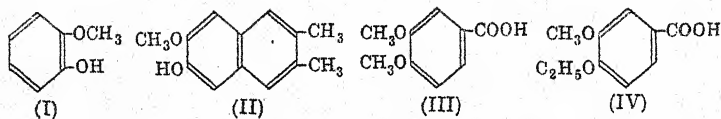


<sup>1</sup> Haworth and Sheldrick, *J.*, 1935, 636.

take place. *l*-Matairesinol (XIV.) which belongs to the diaryl-butane group, can be condensed to yield *l*-conidendrin (XV.), and pinoresinol (XVIII.) through *d*-lariciresinol (XVIII.), both of the tetrahydrofuran group, can be isomerized to *d*-isolariciresinol (XVI.), which in its turn yields *l*-conidendrin dimethyl ether by methylation and oxidation. The structures are shown on p. 379.

#### 4. *d*-Lariciresinol

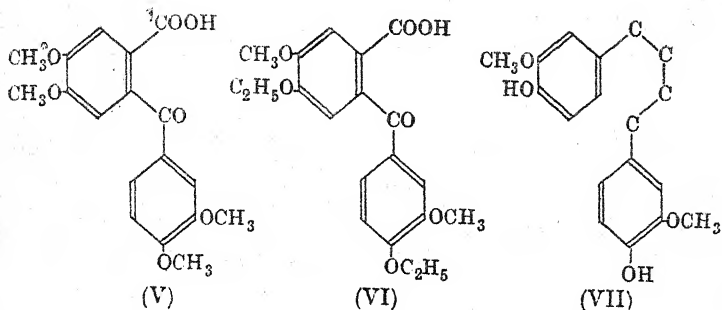
Lariciresinol was first isolated in 1897, from the resin of the European larch (*Larix decidua*).<sup>1</sup> Its structure has recently been made clear and the compound classified as a lignan of the tetrahydrofuran group.<sup>2</sup> Its molecular formula is  $C_{20}H_{24}O_6$ . There are two methoxyl and three hydroxyl groups in the molecule. Two of the hydroxyls are phenolic and the third is primary alcoholic in character. The sixth oxygen atom is inert to carbonyl group reagents, and was consequently thought to be ethereal. This conclusion was supported by the fact that lariciresinol can be isomerized to a compound containing four hydroxyl groups in the molecule. The origin of this additional hydroxyl group is presumably the ethereal oxygen atom. Lariciresinol when heated yields guaiacol (I.) and pyroguaiacin (II.). Methylated lariciresinol can be oxidized by potassium permanganate to veratric acid (III.), and the ethylated lariciresinol to 3-methoxy-4-ethoxybenzoic acid (IV.).



When the isomer of lariciresinol was methylated and then oxidized with permanganate the product was 2-veratroylveratric acid (V.), and the ethylated compound yielded 5-methoxy-4-ethoxy-2(3'-methoxy-4'-ethoxybenzoyl) benzoic acid (VI.).

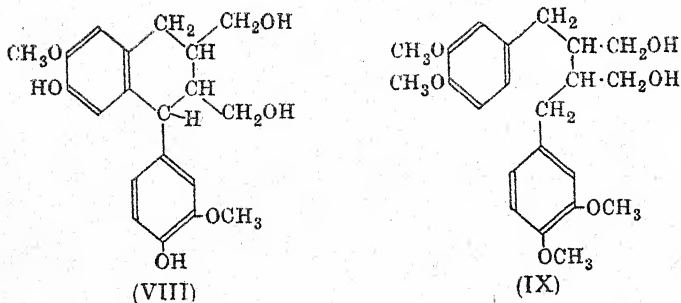
<sup>1</sup> Bamberger, *Monatsh.*, 1897, 18, 481; 1899, 20, 647, 745; 1900, 21, 564; 1902, 23, 1022; 1903, 24, 209; 1917, 38, 457.

<sup>2</sup> Haworth and Kelly, *J.*, 1937, 384.



This behaviour of *isolariciresinol* on oxidation with permanganate is parallel with that of *conidendrin* with the same reagent. *Isolariciresinol* is therefore considered to be, like *conidendrin*, a phenylnaphthalene derivative, and its formation from *lariciresinol* to involve cyclisation of a diarylbutane. The diarylbutane structure for *lariciresinol* is supported by the fact that it yields *pyroguaiacin* (II.) on distillation, just as *guaiaresinic acid*, a diarylbutane, does on similar treatment. The partial formula (VII.) may, therefore, be written down for *lariciresinol*.

When the dimethyl ether of *isolariciresinol* was oxidized with sodium hypobromite it was converted into *l-conidendrin* dimethyl ether.<sup>1</sup>



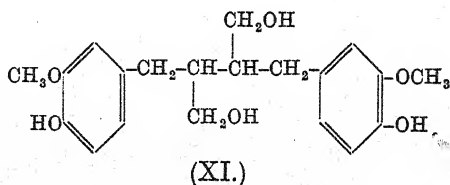
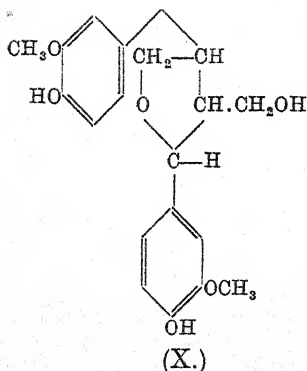
And as *isolariciresinol* contains four hydroxyl groups, two of which only are phenolic; the structure may, therefore, be completed as shown (VIII.).

*Lariciresinol* dimethyl ether can be reduced to the diol,  $\alpha\delta$ -di-(3:4-dimethoxyphenyl)- $\beta\gamma$ -di-(hydroxymethyl)-butane

<sup>1</sup> Haworth and Kelly, *loc. cit.*

(IX.).<sup>1</sup> The relationship of this compound and of *isolariciresinol* to *lariciresinol* indicates clearly that the last-named substance contains an ether linkage in the molecule. No direct evidence has yet been advanced for the tetrahydrofuran linkage in *lariciresinol*, but the properties of the closely related *pinoresinol* and of *lariciresinol* itself make the furan structure more acceptable than any other, such as the propylene oxide arrangement.

*Lariciresinol* may, therefore, be formulated as (X.).



It will be noted that the structure of the diol (XI.) derived from *lariciresinol* is a symmetrical one, and that furan formation from either alcohol group would lead to the same compound.

<sup>1</sup> Haworth and Woodcock, *J.*, 1939, 1054.



## CHAPTER XIII

### SOME THEORIES OF THE NATURAL SYNTHESIS OF VITAL PRODUCTS \*

#### 1. *Introductory*

WHEN we survey that portion of organic chemistry which deals with compounds derived from natural sources, it is impossible to overlook the fact that, although many of these substances can be synthesized in our laboratories, the methods which we employ there differ entirely from those which are utilized in the natural production of the same substances by physiological or phytological means.

The first great difference between the lines of syntheses is found in the ranges of temperature employed in the two cases. In the plant or in the animal body, the reactions which build up extremely complicated products take place, obviously, within very narrow temperature limits; whilst in our laboratories the temperature conditions may vary from one another by as much as 300° C. Not only so, but we press into our service reagents of such instability and reactive power that it is impossible to conceive their coming into existence at all in the animal or vegetable kingdom.

It may be argued that this is only natural. After all, our object in laboratory practice is to obtain the best yield in the shortest time; and a resort to natural methods may be regarded with the same distaste as might be shown by a traveller from London to Inverness at the suggestion that he should tear up his first-class railway ticket and perform his journey on foot. But on the other side there is something to be said also. Very little is as yet known about vital syntheses; and it is quite

\* When this chapter was under consideration, Professor Collie, at my request, sent me a communication embodying some of his views on the subject; and these appeared to me to necessitate the re-writing of the major part of the chapter on the basis of his notes. To avoid continual reference to this private communication and at the same time to indicate his share in the matter, I have placed a † at the beginning of each paragraph which is derived from his notes.—A.W.S.

possible that the methods adopted by the living machine, when we come to understand them, may be simpler and more efficient than our present-day laboratory reactions. Even if this view proves to be erroneous, there can be no doubt that attempts to throw light upon plant and animal methods will broaden our outlook upon organic chemistry as a whole; for at present organic chemists, almost without exception, leave this branch of the subject severely alone.

† One reason for this abstention is perhaps to be found in the manner in which our chemical literature is compiled. In the textbooks of the subject, the naturally occurring substances are not grouped according to their place of origin but are arranged under the headings of alcohols, acids, etc., and are scattered about the literature merely to fill up gaps in long lists of artificially prepared compounds.<sup>1</sup> Organic chemistry of to-day is not properly organic chemistry at all, but has swollen into a chemistry of thousands of carbon compounds which do not occur in nature. Many of these synthetic compounds are the result of the immense industry of chemists who have been misled by the idea that a new compound must necessarily be interesting, and also of the very narrow outlook of certain other chemists who think that a graphic formula is the be-all and end-all of the science.

† Of course the chief reason why in textbooks we find so little information about "how" and "why" certain compounds are produced in plants and animals is because we do not know the answers to the questions involved. In the plant, for example, there appears to be no step-by-step process for making more and more complex materials, as we do in the laboratory. Carbon dioxide, water, and nitrogen, combined or otherwise, are absorbed by the green plant in sunlight. The first substances which can be isolated from the reaction products are sugars, the next ones are the highly complex starches, celluloses, and proteins. All the organic compounds such as acids, esters, fats, colouring matters, and alkaloids are most probably formed by a down-grade process: a decomposition of the starches, celluloses, and proteins. The chemist in his laboratory seeks to make these

<sup>1</sup> Haas and Hill's *Chemistry of Plant Products* gives an excellent survey of the "organic" field, and should be consulted by any one who desires to go further into the subject.

compounds by syntheses from simpler bodies ; the plant appears to produce them by a reverse operation from stored-up material of an extremely complex molecular structure.

† Some of these down-grade processes can be followed to a certain extent in the laboratory. Celluloses, starches, and proteins can be hydrolysed, oxidized, or otherwise decomposed. But our methods, as a rule, are too violent ; and the fine grades of reaction which take place slowly at ordinary temperatures in plants have, up to the present, defied imitation in the laboratory.

† Nevertheless we must not lose sight of the fact that although natural reactions often *seem* to operate in a way quite different from laboratory reactions, yet both sets must obey the same laws. Therefore, if we find that in the synthetic processes of our laboratories certain lines are followed under conditions which could exist in plants, we are not far wrong in assuming that, in the down-grade processes of nature, the same general direction will be taken in the formation of products.

† Another point arises here. All reactions which are likely to be employed in vital syntheses are reversible ; and hence if they be carried out in glass test-tubes they must come to an equilibrium point, except in those cases wherein gaseous products are formed. How, then, does the plant succeed in producing its high yields of certain substances which, in a test-tube, would be formed only in minor quantities from the same reagents ? When we examine the living plant, we are at once struck by the wonderful mechanism of the natural chemical laboratory which we find there. It is a system of test-tubes made of cellulose and differing from ordinary test-tubes in that the walls are constructed from semi-permeable membranes. Each cellulose test-tube is immersed in a solution differing from that which is contained within the cellulose vessel. The membrane acts not only as a container, as the glass test-tube does, but in addition it behaves as a filter, a concentrator, or a separator. Thus during the progress of a down-grade reaction in which a complex molecule is broken up into constituent parts, the cellulose wall permits a certain product to accumulate in one part of the plant whilst a mixture of other compounds may be withdrawn to a different region. In this way the ordinary equilibrium stage of the reaction is evaded ; and much higher yields may thus be attained.

† But what starts this down-grade process? Once the plant has synthesized its starches, etc., why are these substances not stable, as they are when we place them in bottles in a chemical museum? To answer this question we must know how the plant grows; and what is meant by a living material as opposed to dead matter. The differences between the two are much too marked to allow of dispute.

† When a crystal grows in a solution, we may regard the process as the first glimmering of individual life in that particular substance. Infinitely more complex is the growth of protoplasm from carbon, hydrogen, nitrogen, and oxygen; the smallest particle of protoplasm is inconceivably greater than the atoms from which it has been built up. Still more complex is the growth of a plant from the seed. In all these cases a directive agency seems to be at work. Whether further investigation will or will not show that all these phenomena can be explained by purely chemical and physical laws, time alone can show; but it is quite certain that at present the only scientific course is to admit that we do not know. The chemical reactions which take place in the living plant are in certain respects ~~se~~ different from those which go on in the laboratory that we are forced to recognize the action of some subtle agency which, up to the present, we have been unable to imitate.

† Let us return to the degradation of the starches, celluloses, and proteins. The plant, under the action of sunlight, has stored these substances in its body and has grown to its full size. The directive force begins to get exhausted; the plant is growing old; most of its starches are now used up; and the celluloses and proteins are beginning to undergo more and more rapid decomposition. The down-grade process has set in with increasing velocity. The plant is still alive, but the system is losing instead of gaining energy. Fermentations have begun; but fermentations will only explain a part of the process, for they are catalytic reactions which would, normally, reach their equilibrium stages whether the plant were young or old. The enzymes causing them are chemical reagents which enable part of the stored-up energy in the plant to be set free again; but the actual disturbance of equilibrium is due to the separation and segregation of the reaction products by the semi-permeable membranes.

It seems not impossible that the later stages in the life-history of a plant are brought about by some change in the nature of its cell-walls, akin, perhaps, to the ossification of arteries which sets in within the animal body under somewhat similar conditions. If, at this stage, the cells ceased to act as semi-permeable membranes, the whole machinery of the plant would become choked with by-products, and the natural changes which are necessary in living matter would gradually come to an end.

† During the growing phase of the plant, starches, cellulose, proteins, and enzymes are produced; but as the plant ages, the growing energy lessens, the enzymes get the upper hand and prey upon the substance of the plant. They are the parasites which finally kill their parent.

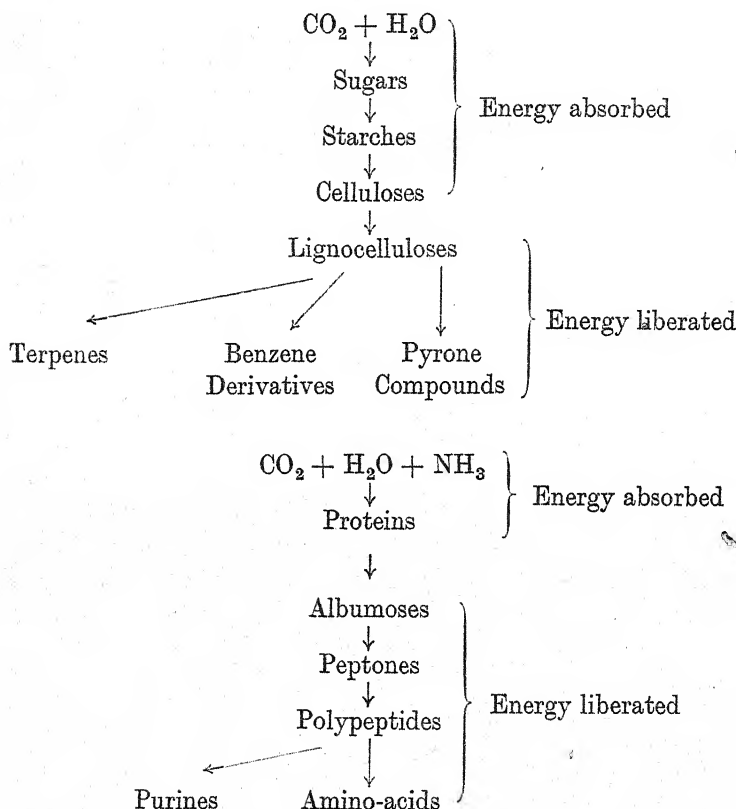
† Considering the importance of the ferments in the scheme of nature, it is extraordinary to notice how very briefly they are referred to in most textbooks of organic chemistry;<sup>1</sup> and the textbook reflects to a great extent the outlook of the average organic chemist. It is hardly to be wondered at if the new generation of organic chemists, trained by such methods, becomes imbued with an almost superstitious reverence for the deluge of organic compounds which have been spawned in thousands in chemical laboratories for, apparently, no useful purpose whatever.

## 2. *The General Course of Vital Syntheses and Degradations*

† When the action of the living machine is considered in its broadest aspects, there seems to be no doubt that it can be regarded as divisible into two opposed processes. In the first group come the synthetic reactions by means of which the products assimilated by the plant or animal are converted into extremely complicated celluloses and proteins; whilst in the second class are placed those decompositions and changes which convert the celluloses and proteins into simpler substances. The first series of reactions are probably carried on with the absorption of external energy; the second group comprises reactions which liberate this energy once more. It may be

<sup>1</sup> Haas and Hill, in their *Chemistry of Plant Products*, give a very good summary of the nature of enzymes and their action in plants. See also Bayliss, *Nature of Enzyme Action*.

convenient at this point to give a table indicating the course of vital action in the two cases:—



In the cellulose synthesis, the reactions lead to the formation of long chains built up from sugar molecules; for hydrolysis of cellulose yields simple carbohydrate derivatives almost unaltered. In this case—after the initial production of formaldehyde—the reactions are obviously quite uncomplicated and appear to be simple polymerization and dehydration.

The transformation of the celluloses into lignocelluloses is evidently more complex, as the latter compounds appear to contain cyclic nuclei of various types; and from them the aromatic and heterocyclic substances formed in plants may be produced by a series of degradation reactions.



Turning to the proteins the same holds good in general. The first stage must be the formation of simple amino-compounds which have not yet been isolated and proved to take part in the synthesis. From these, by dehydration, the proteins are formed. After this, fermentation yields simpler substances which are classed as albumoses. Further degradation yields peptones, which are closely akin to the albumoses; and finally the material breaks down into polypeptides and simple amino-acids.

### 3. Possible Reactions in Vital Syntheses

In attempting to deduce the actual processes which lead to the formation of natural products, we are faced by two facts. In the first place, we are able to rule out as impossible such reactions as depend upon high temperatures and violent reagents; but, in the second place, we are not entitled to assume that, because up to the present we have not succeeded in making a reaction "go" at ordinary temperatures, it is therefore impossible for such a reaction to proceed effectively under these conditions. The safest course is obviously to confine ourselves as far as possible to reactions involving mild reagents and capable of proceeding economically at ordinary temperatures; though at the same time we need not exclude other reactions entirely.

Limiting ourselves thus, the choice before us is by no means so restricted as might at first be expected. Polymerization, condensation, hydrolysis, hydration and other addition reactions, dehydration, oxidation, reduction, and intramolecular change are all reactions which are known to be capable of taking place at ordinary temperatures.

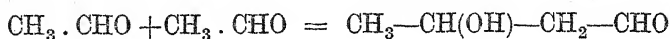
With regard to polymerization the data are too numerous to need reference in detail. The polymerization of aldehydes, the production of truxillic acid from cinnamic acid under the action of light, the conversion of ethylene into higher hydrocarbons and the synthesis of rubber from isoprene are too well known to render it necessary to discuss them.

When we come to condensation the matter demands a more careful scrutiny; for various types of reaction are involved, each of which has a particular application to the problem before us.<sup>1</sup>

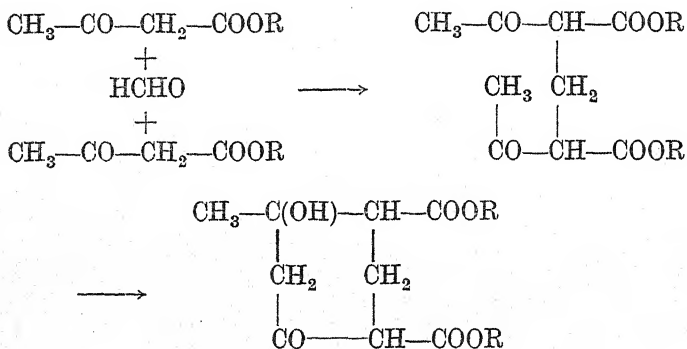
<sup>1</sup> See Baeyer, *Ber.*, 1870, 3, 63.



The aldol condensation <sup>1</sup> can be carried out with the help of traces of foreign materials; and it is noteworthy that among these catalysts are to be found salts such as the acetates, carbonates, and bicarbonates of the alkalis, all of which might be found in the saps of plants.\* Now the aldol condensation not only provides a means whereby carbon chains may be formed from shorter groups:

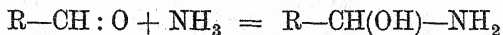


but in addition it also gives rise to carbocyclic derivatives: <sup>2</sup>



The benzoin condensation might also be reckoned as a probable vital reaction, for, although it is usual to employ heat in the laboratory, it seems evident that this condensation proceeds at ordinary temperatures at a slower rate.

The second class of condensation under consideration includes those reactions in which ammonia molecules or their substitution products take part. Of these, apart from amide formation the most important is the production of amino-alcohols from aldehydes:



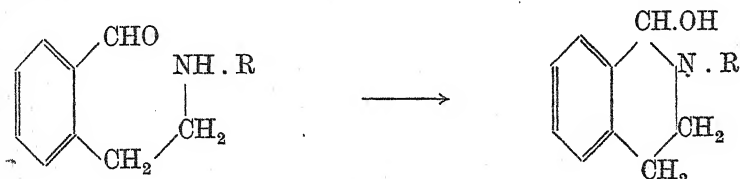
An intramolecular application of this reaction, in which an

<sup>1</sup> See Robinson's suggestions on this point (*J.*, 1917, 111, 876); compare Raper, *J.*, 1907, 91, 1831.

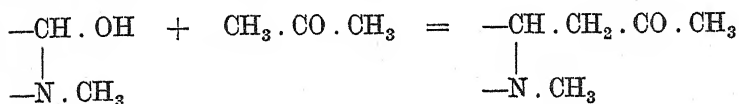
\* The actual catalyst may be the hydroxyl ion.

<sup>2</sup> Rabe, *Annalen*, 1898, 360, 265.

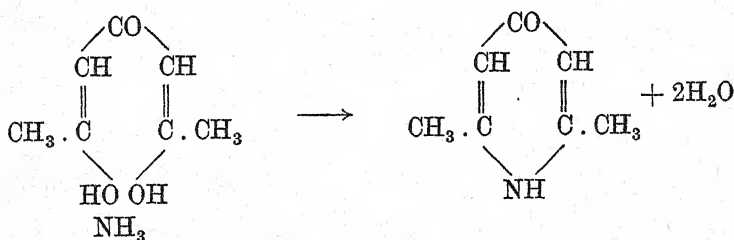
amino-aldehyde is employed, leads to ring-formation and the production of an amino-alcohol of the following type:—



And, as Robinson <sup>1</sup> has shown, these amino-alcohols react readily in aqueous solutions with ketones, producing new derivatives by the elimination of water:



Different in nature is the ring-formation produced when such substances as diacetylacetone are treated with ammonia.<sup>2</sup> Here one molecule of ammonia interacts simultaneously with two hydroxyl radicals—the ketone enolizing—in order to produce a derivative of pyridine:



Turning to the question of hydrolysis, it is unnecessary to dwell at length upon the ordinary reactions. Attention must be drawn, however, to the fact that the same reagents may produce different end-products according to the conditions employed. Thus acetoacetic ester derivatives may yield either a ketone or an acid in addition to acetic acid, in the ordinary acetoacetic ester synthesis.

The most important reagents in this field, however, are the enzymes; and it may be worth while to deal with their action

<sup>1</sup> Robinson, *J.*, 1917, 111, 876.

<sup>2</sup> Collie, *J.*, 1907, 91, 1806.

in more detail. For the hydrolysis of the proteins, two classes of enzyme are known, which are termed proteolytic. The members of the pepsin group attack albumins only in weak acid solutions, converting them into albumoses and peptones, which are soluble albuminous compounds of complicated structure. The trypsin group members, on the other hand, act only in neutral or weakly alkaline solution. A third class of enzymes, the lab-enzymes, have the faculty of coagulating protein compounds and are therefore termed coagulating enzymes. To some extent a fourth type of enzyme might be included in this section, since its reaction resembles those of the proteolytic class in so far that it depends upon the hydrolysis of the amide group. This last type has the faculty of breaking down urea and uric acid derivatives. The lipolytic enzymes are utilized to break down fats, from which they liberate glycerine. They appear to react best in acid solution.

Several enzymes are known which can be employed to hydrolyse such materials as starch; and the progress of the hydrolysis depends upon the enzyme chosen. Thus when diastase acts upon starch it converts it into soluble material and breaks it down eventually to simple carbohydrates, the end-product being maltose,  $C_{12}H_{22}O_{11}$ . The application of maltase carries the process a stage further, two molecules of glucose being formed. Cane-sugar is broken down by invertase to glucose and fructose.

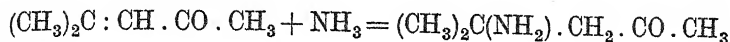
In all these cases, of course, the enzyme acts merely as a catalytic agent and has no influence upon the equilibrium point. Thus, as has been mentioned in a previous chapter, chlorophyllase may be employed either to hydrolyse a phytol ester or to replace the phytol radicle by an ethyl group.

Under the head of addition reactions it is only necessary to mention one or two processes. Among the unsaturated compounds, and especially in the terpene group, water can be added on to double bonds at ordinary temperatures when acids are present.<sup>1</sup> Apparently the reaction takes place in two stages: a molecule of acid first attaching itself to the double linkage in order to form an ester which is then hydrolysed, leaving an alcohol.

Under ordinary conditions also, ammonia has the faculty of

<sup>1</sup> Wallach, *Annalen*, 1908, 360, 102.

attacking certain ethylenic linkages. Thus mesityl oxide takes up a molecule of ammonia to form diacetonamine :



Dehydration is a reaction capable of almost endless application in the field of vital chemistry. Saturated compounds may be converted into unsaturated derivatives ; carbon chains may be formed, as in the mesityl oxide and phorone syntheses ; benzene derivatives and heterocyclic substances such as pyrones can be prepared without exceeding ordinary temperatures. Indeed, it seems probable, though not proved, that a large proportion of vital syntheses depend upon successive dehydrations and rehydrations, by means of which the structure of the molecule can be altered.

As to oxidation and reduction, no doubt can be entertained as to the prominent part taken by them in vital reactions. As far as oxidation goes, we are acquainted with numerous enzymes (oxidases) which act as agents in the reactions of living tissue ; and though the nature of the corresponding reducing enzymes, the reductases, has not been fully studied, there seems to be no question about their existence. Apart from enzyme action, numerous cases of spontaneous oxidation are known to the organic chemist, such as the formation of indigo from indoxyl and the production of oxyhæmoglobin from hæmoglobin.

Intramolecular change is a branch of the subject which it is hardly necessary to treat in detail ; but the pinacone change, the Beckmann rearrangement, and the benzilic acid change may be mentioned, since they may serve to throw light upon vital reactions. The most important of all is the keto-enol rearrangement ; but this will be fully described in a later section.

In Volume I. of this book we have already encountered some examples of an intramolecular rearrangement which is of the greatest importance from the point of view of natural terpene syntheses ; the formation of cyclic compounds from open-chain di-olefinic derivatives. The cases of citronellal and *isopulegol* ; rhodinal and menthone ; citral and *cyclo-citral* ; and the conversion of geraniol, nerol, and linalool into terpeneol, are examples of the type to which we refer. These changes take place either spontaneously or under the influence of alkali or acid ; and it

seems not improbable that some such rearrangement leads to the production of terpenes in nature.

Among natural products, methylamine derivatives occur; and it appears probable that these are formed by the action of formaldehyde:—



In laboratory practice the reaction takes place even at the temperature of a water-bath; so that it evidently can be carried out, though slowly, under ordinary conditions.

Photochemical effects must, of course, play a very striking part in vital processes, especially in the vegetable kingdom. Of these, the most important from the theoretical standpoint is the discovery by Cotton<sup>1</sup> that the dextro- and lævo- forms of tartaric acid absorb *d*-circularly polarized light to different extents; which implies that such light will decompose them at different rates. Now since light is circularly polarized by the surface of the sea, we have a natural method whereby the production of unequal quantities of asymmetric material can be attained; and once the balance between the two isomers is thus disturbed, the general production of optically active compounds becomes possible. It may be that these experiments indicate the manner in which optically active substances first made their appearance on the earth's surface.

#### 4. *The Production of Carbohydrates*

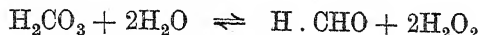
Since the carbohydrates form so large a proportion of plant tissues and so important a group of animal foodstuffs, it is natural that much speculation has been directed to the question of how these materials come into existence as a result of biochemical syntheses. As to the source from which the carbon is drawn, there is no dispute: the living plant is believed to obtain it from the surrounding atmosphere in the form of carbon dioxide or carbonic acid.

Strangely enough, the next stage in the process is the one which has given rise to most controversy, and even at the present day there is much dispute as to the exact mechanism involved in

<sup>1</sup> Cotton, *Ann. Chim. Phys.*, 1896, VII., 8, 373.

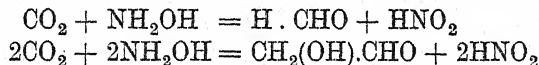
the changes which undoubtedly take place.<sup>1</sup> It will suffice here to indicate some of the suggestions which have been put forward.

The simplest hypothesis rests on the assumption that water and carbon dioxide may undergo a process of mutual oxidation and reduction.

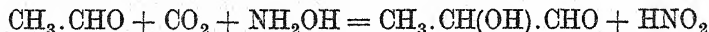


If, now, an enzyme were present in the plant which has the power of decomposing hydrogen peroxide,<sup>2</sup> the reaction's main course would be from left to right in the equation above, and a steady production of formaldehyde would occur in the leaf. The energy required to furnish driving-power in the reaction must be drawn originally from solar radiation; but the immediate cause of the transformation might possibly be found in the electrical conditions on the leaf-surface.<sup>3</sup> Unfortunately for this view, the presence of hydrogen peroxide in leaves<sup>4</sup> has not been confirmed.<sup>4</sup>

Another hypothesis<sup>5</sup> depends upon the assumption that hydroxylamine plays a part in the process. This hydroxylamine is supposed to be present in the leaf as a result of the reduction of nitrates absorbed by the plant as part of its nutriment. The reactions postulated are as follows:



These products have actually been detected in the leaves of the elder. Now the glycollic aldehyde formed in the second reaction is assumed to be reduced to acetaldehyde; and a further stage of carbon dioxide absorption ensues, yielding lactaldehyde:



These materials exist in the leaves of the poplar. Obviously processes of this sort might be utilized to explain the production of complex carbohydrate structures.

<sup>1</sup> See Jörgensen and Stiles, *Carbon Assimilation*; Meldola, J., 1906, 89, 745; Moore, J., 1921, 119, 1555; Haas and Hill, *The Chemistry of Plant Products*.

<sup>2</sup> Loew, *Ber.*, 1902, 35, 2487.

<sup>3</sup> Gibson, *Ann. Botany*, 1908, 22, 117.

<sup>4</sup> Molisch, *Biochem. Z.*, 1921, 125, 257.

<sup>5</sup> Mazé, *Compt. rend.*, 1921, 172, 173.



Willstätter and Stoll,<sup>1</sup> from a study of chlorophyll, arrived at the following conclusions. Chlorophyll acts not only as a sensitizer in photochemical reaction, but it plays a direct part in the break-down of carbonic acid. A stage in the process is the formation of a labile addition-product of chlorophyll which may be built up either from carbonic acid itself or from one of its derivatives. According to Willstätter and Stoll, the action of light is to loosen the bonds of the carbonic acid molecule and thus bring about isomeric change into per-formic acid or formaldehyde peroxide. By enzymatic action, these compounds then lose some of their oxygen. Whether formaldehyde is the actual produce of the process is left in doubt; for even the detection of formaldehyde in the leaf is not sufficient to show that it is an intermediate-product in assimilation, since it might also occur as a result of reactions totally unconnected with the reduction of carbonic acid.

Somewhat similar views of the mechanism were put forward by Spoehr and McGee,<sup>2</sup> whose results indicate that the leaf contains something which chemically absorbs carbon dioxide and which they believe to be a protein.

An hypothesis which inverts the usually accepted sequence of things is due to Wo. Ostwald,<sup>3</sup> who suggests that the photochemical reaction is one of photo-oxidation instead of photo-reduction. He assumes that the first stage in the process takes the form of the production of a compound of a protein with carbon dioxide. This is accompanied by the autoxidation of a lipid with the formation of a lipid peroxide which is sparingly soluble in water.<sup>4</sup> Interaction of the protein-carbon dioxide compound and the lipid peroxide in presence of water is supposed to lead to the production of formaldehyde and oxygen; and the lipid-peroxide is regenerated by autoxidation. The whole process is supposed to take place at a protein-lipid boundary surface. On Ostwald's hypothesis the part played by chlorophyll is simply that of a promoter in the autoxidation of the lipid.

Turning to purely photochemical experiments, the evidence

<sup>1</sup> Willstätter and Stoll, *Untersuchungen über die Assimilation der Kohlensäure* (1918).

<sup>2</sup> Spoehr and McGee, *Science*, 1924, 59, 513.

<sup>3</sup> Wo. Ostwald, *Kolloid-Z.*, 1923, 33, 356.

<sup>4</sup> Compare Gallagher, *Biochem. J.*, 1923, 17, 515; 1924, 18, 29, 39.



proves somewhat confusing. Usher and Priestley <sup>1</sup> reported that by exposing a saturated solution of carbon dioxide in a quartz tube to the action of ultra-violet light they obtained an easily recognizable quantity of formaldehyde, mostly in the polymerized form. Berthelot and Gaudechon,<sup>2</sup> on the other hand, were unable to detect formaldehyde as an end-product of the action of ultra-violet light on carbonic acid except when hydrogen was present. This was supported by the work of Stoklasa.<sup>3</sup> Baly, Heilbron and Barker <sup>4</sup> state that formaldehyde may be produced from carbon dioxide and water by purely photochemical means. According to their results, formaldehyde is formed in aqueous solutions of carbon dioxide under the influence of light of short wave-length ( $\lambda = 200\mu\mu$ ) as well as by visible light in presence of visibly coloured substances which have the power of forming labile additive compounds with carbonic acid. Spoehr <sup>5</sup> has been unable to confirm these results.

If it be assumed that formaldehyde is the primary product in the course of carbohydrate syntheses, two questions present themselves immediately. (1) Can the plant tolerate formaldehyde? (2) How is formaldehyde converted into its higher polymerides?

With regard to the first question, formaldehyde is undoubtedly a poison for some of the lower plant organisms; but it can be assimilated by others <sup>6</sup>—e.g., the *Tropaeolum majus* <sup>7</sup>—without injury. And in any case, if the polymerization of the aldehyde proceeds at a velocity comparable to that of its synthesis, there is no need to assume that at any moment there will be more than a trace of the poison present in the plant-organism. This is justified by the fact that it was only with great difficulty that the presence of any formaldehyde in the leaf could be established,<sup>8</sup> which indicates that the aldehyde must be polymerized almost immediately after its formation.

<sup>1</sup> Usher and Priestley, *Proc. Roy. Soc.*, 1911, **84**, [E], 101.

<sup>2</sup> Berthelot and Gaudechon, *Compt. rend.*, 1910, **150**, 1690.

<sup>3</sup> Stoklasa, *Monatsh.*, 1911, **32**, 53; *Biochem. Z.*, 1912, **41**, 333.

<sup>4</sup> Baly, Heilbron and Barker, *J.*, 1921, **119**, 1025.

<sup>5</sup> Spoehr, *J. Amer. Chem. Soc.*, 1923, **45**, 1184; compare Baly, Heilbron and Barker, *Nature*, 1923, **112**, 323.

<sup>6</sup> Sabalitschka and Riesenbergs, *Biochem. Z.*, 1924, **144**, 545, 551; **145**, 373.

<sup>7</sup> Jacoby, *Biochem. Z.*, 1922, **128**, 119.

<sup>8</sup> Gibson, *Ann. Botany*, 1908, **22**, 117.

It is now necessary to consider the second problem and see what sort of mechanism can be suggested for the conversion of formaldehyde into its higher polymers. In earlier days it was believed that cane sugar was the first recognizable carbohydrate produced by carbon assimilation in the plant;<sup>1</sup> but more recent investigations<sup>2</sup> lead to the conclusion that sucrose alone is detectable in the non-green parts of variegated leaves, whilst in the green parts monoses were discovered. Further, when full-grown leaves of pelargonium were entirely depleted of sugar by keeping the plants in the dark and were subsequently exposed to light, the first sugars identified were monoses; and it was only later that sucrose and starch were formed. From this it seems that monoses are really the first products, and that the appearance of sucrose is a secondary stage in the process.

The polymerization of formaldehyde to fructose was long ago shown to be brought about by the action of calcium hydroxide in dilute solutions;<sup>3</sup> and Baly, Heilbron and Barker, by acting on a solution of carbonic acid with ultra-violet light, obtained a product which was examined by Irvine and Francis<sup>4</sup> and found to contain about 10 per cent. of a hexose.

These results, though interesting in themselves, have little bearing on the actual production of the carbohydrates in the living plant; for the laboratory-produced sugars are racemic, whereas the products of biochemical action are optically active. This fact differentiates the two processes in a decisive manner since it shows that in the phytological production of the sugars an asymmetric agent comes into play at some stage in the action.

Two possible explanations suggest themselves for the occurrence of the active sugars. In the first place, the agent which stimulates the polymerization of the formaldehyde may itself be asymmetrical (an enzyme); and thus one enantiomorph may be formed in greater quantity than the other: or possibly the racemic sugar is produced by direct methods and is then acted upon by a selective enzyme such as are common in plants, with the result that one antipode is more rapidly decomposed

<sup>1</sup> Brown and Morris, *J.*, 1893, 62, 604.

<sup>2</sup> Weevers, *Proc. K. Akad. Wetensch. Amsterdam*, 1934, 27, 46.

<sup>3</sup> Loew, *J. pr. Chem.*, 1886, 33, 321; Fischer and Passmore, *Ber.*, 1889, 22, 359.

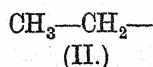
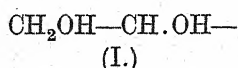
<sup>4</sup> Irvine and Francis, *J. Ind. Eng. Chem.*, 1924, 16, 1019.

than the other. In either way a preponderance of one active form would result. It must be frankly admitted that even in this simple problem we can only say that we do not know the true solution.

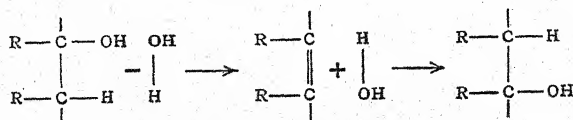
With the production of sugars of the hexose type, however, the main difficulties are ended: for by the action of enzymes these can be converted into much more complex materials, the polysaccharides;<sup>1</sup> and even higher complexes such as dextrin can be produced from the hexoses by catalytic means. As to the further stages by which cellulose and its analogues are formed, we can only admit our ignorance; though the fact that these substances can be reduced to simpler materials by catalytic action certainly suggests that they are probably built up by a similar process.

### 5. Collie's Theory of Enzyme Action

† During the break-down of certain carbohydrate derivatives under the action of enzymes, an important step in the reaction is evidently the accumulation of hydrogen atoms at one end of the chain and the gathering of oxygen atoms at another point. Only on this assumption can we explain the conversion of the radicle (I.) into the grouping (II.) which evidently takes place during alcoholic fermentation:—

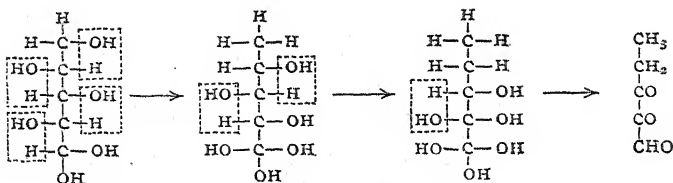


Now if the sugar molecule be regarded as being built up from a chain of carbon atoms united with water molecules, such a transformation can readily be represented by a mere change in orientation of the hydrogen and hydroxyl radicles, which might be produced by dehydration and rehydration:—



<sup>1</sup> Hill, J., 1898, 73, 634; see also Bayliss, *The Nature of Enzyme Action*.

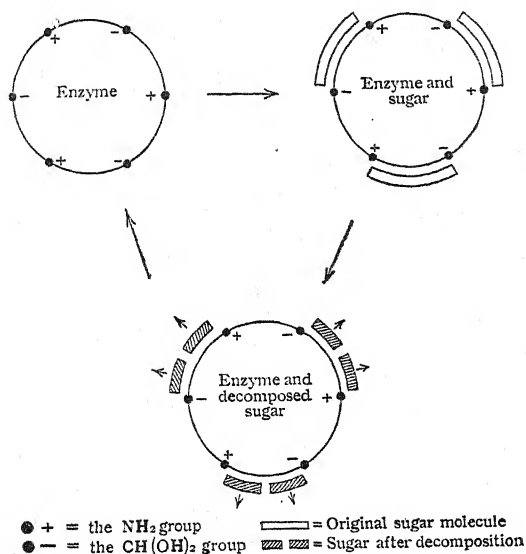
† In the case of a pentose, distinguishing the inverting groups by the dotted lines, we should get the following picture :—



† Take the case of a hexose as an illustration of the next step in the argument. At one end of the chain is the weakly basic hydroxyl group, whilst at the other end lies the aldehyde radicle, which, in its *ortho*-form, is weakly acidic. It is therefore reasonable to assume that the main chain of the sugar is subjected to electrical strain. Now if this electrical condition can be interfered with, changes might be expected to occur in the molecule; and it is possible that the enzymes work in this manner. The enzyme molecule is probably built up from amino-acids somewhat in the same manner as a protein; so that it contains, like the sugar, a basic group ( $-\text{NH}_2$ ) and an acidic radicle ( $-\text{COOH}$ ). From what we know of their molecular complexity, the enzyme molecules must be immensely greater than the molecules of simple carbohydrates; and it is therefore probable that one molecule of enzyme may react simultaneously with hundreds of carbohydrate molecules. The basic and acidic groups of the sugar will come into contact with the acidic and basic portions of the enzyme *provided that these groups occupy suitable positions in space*; \* the system is then short-circuited; and what might be termed "molecular electrolysis" results; the energy of the sugar molecule is set free as heat; and, by the rearrangement of the hydrogen and hydroxyl groups of the sugar, new compounds are formed which are no longer capable of combining with the amphoteric enzyme. The latter may then be recharged by induction or by the presence of ions in the solution, as is the case with many colloids.

The following diagram represents the various steps in the process :—

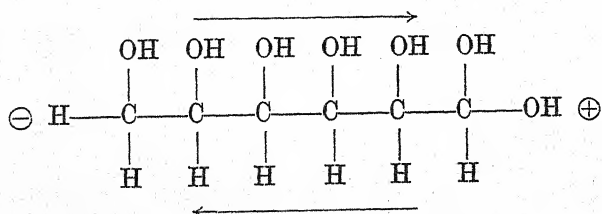
\* This serves to explain the selective power of enzymes.



In its elements the Collie theory bears a strong resemblance to Ehrlich's side-chain theory of toxins and anti-toxins, the two groups at the points attacked being analogous to Ehrlich's receptors, whilst the corresponding points in the enzyme are akin to Ehrlich's haptophore groups.

With slight modification, Collie's theory would furnish a mechanism for the polymerization of formaldehyde to optically active sugars.

† Another possibility must not be left out of account. When we examine the structural formula of a sugar in its *ortho*-form the similarity between it and one of the usual diagrams to illustrate electrolysis strikes the eye at once :



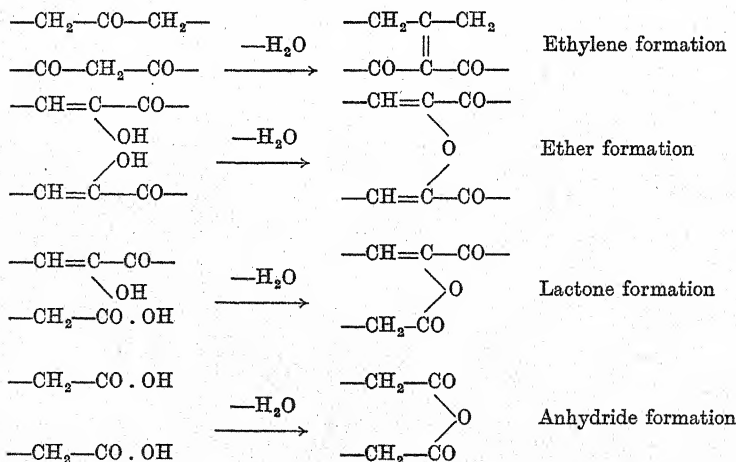
Now if we imagine a pair of terminals inserted in the molecule as shown by the + and - signs, it is clear that the hydrogen atoms would be drawn to the left, whilst the hydroxyl groups

would move to the right. This would give us the same accumulation of hydrogen atoms at one end and hydroxyl groups at the other. Collie's conception of the action of enzymes allows us to picture the necessary electrical terminal inserted into the molecular structure of the sugar; and it may be noted that these terminals do not necessarily attack the two ends of the chain; they might quite as easily be supposed to be inserted at any point in the molecular structure which is spatially suitable for this entry; and in this way the selective action of different enzymes may be accounted for.

### 6. The Polyketide Group

Since the addition of water to some molecules and the removal of it from others are two of the most important reactions in the chemistry of vital processes, it is worth while to examine the known behaviour of certain atomic groupings which show a marked inclination towards these two reactions.

It may be recalled that the polyketides\* have the general formula  $H.(CH_2.CO)_n.OH$ . The higher members of the series therefore contain the carboxyl radicle,  $-COOH$ , and also the grouping  $-CO-CH_2-CO-$ , which is capable of enolization into  $-C(OH):CH-CO-$ . From these three groupings water can be removed in four different ways, as shown in the formulæ below.

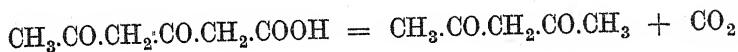


\* See Vol. I. A general account of the polyketide reactions is given by Collie, *J.*, 1907, 91, 1806.



It is hardly necessary to point out that the last three reactions are easily reversible, since the addition of water to anhydrides, lactones, and ethers of this special type is familiar. The first reaction is also a reversible one in a number of well-known cases, among which the break-down of pulegone into acetone and methyl-*cyclohexanone* may be quoted.

The higher members of the polyketide group have another property which deserves mention here: the ease with which they lose carbon dioxide and yield ketones. The production of acetone from acetoacetic acid is the simplest instance of this; and triacetic acid acts in the same way, giving acetylacetone:

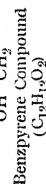
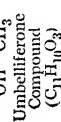
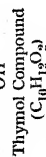
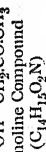
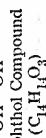
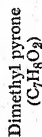
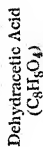


Finally, they react readily with ammonia, yielding amino-derivatives like  $\beta$ -amino-crotonic acid or imino-compounds of the pyridine group.

From this it is obvious that the polyketides form one of the most reactive classes known to organic chemistry; and a glance at the table on p. 404 will give some idea of the number and variety of compounds, akin to natural products, which can be obtained from a single polyketide derivative, dehydracetic acid.

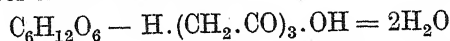
In the following sections of this chapter, an attempt will be made to show how it is possible to link up genetically the polyketide group with a large number of the more important groups of natural products such as the carbohydrates, the benzene series, the anthocyanins and other plant pigments, the alkaloidal series, and the fats. It seems advisable to call the attention of the reader to the remarkable way in which the polyketide skeleton can be traced in detail through so many of the natural products, even of complex character; and throughout the remainder of the chapter it should be borne in mind that the raw material of the plant is cellulose, since from its degradation are obtained all the more important plant products. The connection between the carbohydrates and the polyketides is therefore of the greatest importance; and it will be dealt with in the next section.



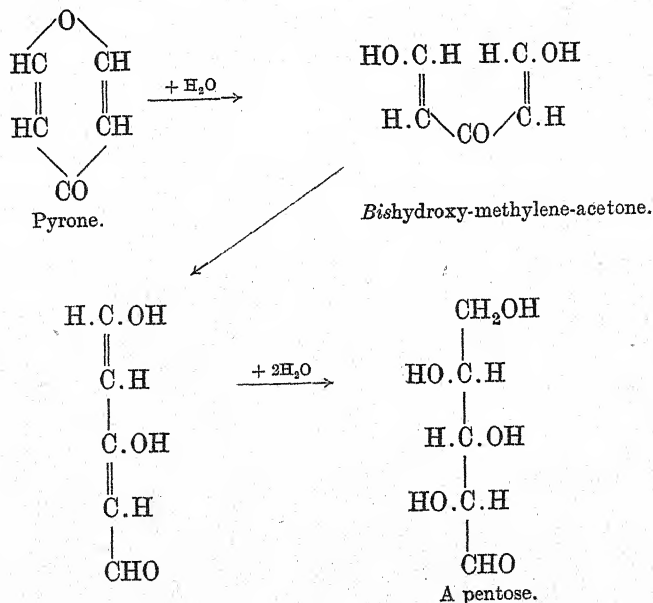


## 7. The Relations between the Carbohydrates and the Polyketides

† When a carbohydrate is compared with a polyketide having the same number of carbon atoms, it is clear that since both structures are built up from straight carbon chains, the main difference between them must lie in the oxygen and hydrogen atoms of their formulæ. On comparing, for example, a hexose with the triketide, triacetic acid, it becomes clear that the two formulæ differ from each other by the elements of a round number of water molecules:



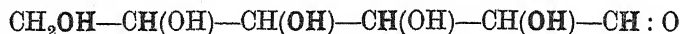
Now consider the polyketide derivative pyrone. This is acted upon by metallic alcoholates with the formation of derivatives of bishydroxy-methylene-acetone.<sup>1</sup> The proper conditions for carrying out a similar reaction with a water molecule instead of one of sodium ethylate have not yet been discovered; but the point is not without theoretical interest, as it suggests a means whereby sugars may be converted into polyketides and *vice versa*. Taking pyrone as an example, the following stages would be involved:—



<sup>1</sup> Willstätter and Pummerer, *Ber.*, 1905, 38, 1461.

A reverse series of reactions would lead from the carbohydrates to the polyketides and thence to all the classes of compounds which were enumerated in the last section.

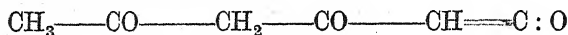
A simpler, though less probable, way of formulating the conversion of a carbohydrate into a polyketide, and *vice versa*, is shown in the following formulæ. For the sake of clearness, the hydrogen atoms and hydroxyl groups involved in the first dehydration reaction are printed in heavy type. Starting with, say, glucose :



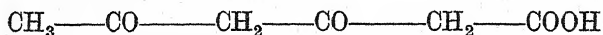
removal of three molecules of water would lead to the production of the following structure :



which is the enolic form of :



and from this the polyketide could be obtained by the addition of an extra molecule of water :



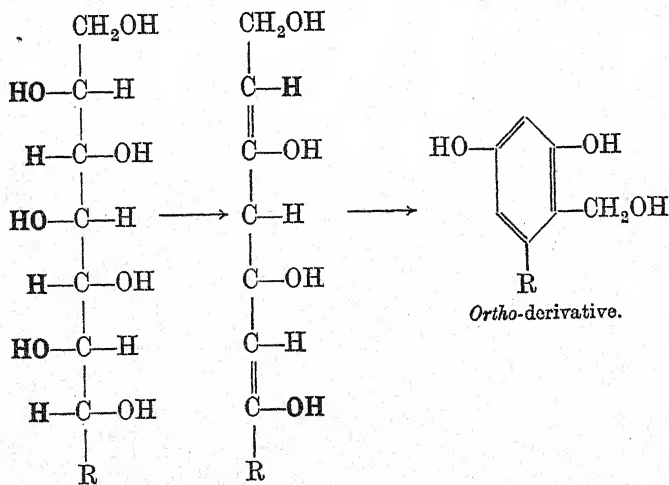
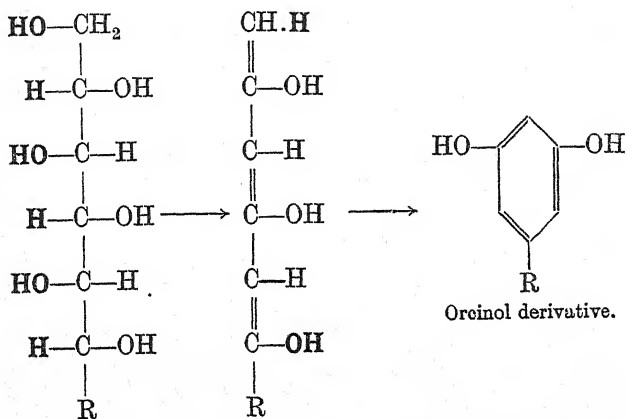
Now, though it must be frankly confessed that up to the present our laboratory methods have failed to bring about either of these conversions,\* there are numerous facts tending to show that many plant products are derived from polyketide chains; and since the carbohydrates form the most obvious source of polyketide derivatives it seems not unwarranted to assume that reactions similar to the above do take place in plants. If we do not make this assumption, we require so many different postulates in devising syntheses of vital products that the matter becomes extremely complicated; whereas by granting the possibility of polyketide production it may be rendered very simple.

### 8. The Carbohydrates, Polyketides, and Benzene Series

† The aromatic series is strongly represented among plant products; and it seems evident that the source of the vegetable

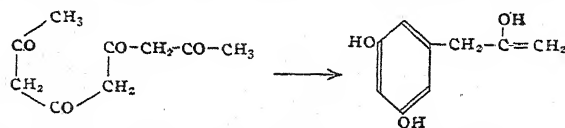
\* One great difficulty in the way is the ease with which open-chain derivatives of the polyketide series are hydrolysed in presence of alkali or acid.

benzene compounds must be sought in the carbohydrates of the plant. The formulæ below indicate how benzene derivatives might be produced direct from the carbohydrates by means of simple dehydration followed by intramolecular rearrangement. Only two examples are given, as they are intended as illustrations and not as a complete list of possible changes. The groups involved in the dehydrations are printed in heavy type.



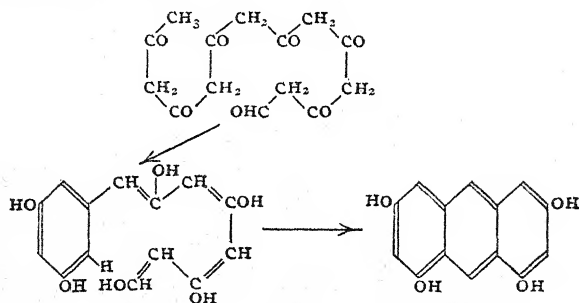
† If the production of polyketides from the carbohydrates be assumed in order to simplify the formulæ, the following

scheme shows how unsaturated side chains attached to benzene nuclei could be formed by dehydration and rearrangement :—



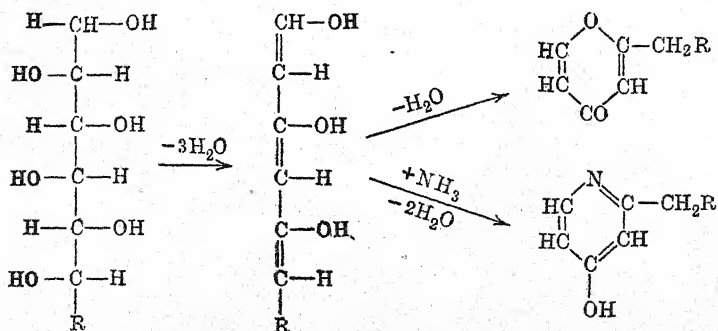
from which, by enzymatic reduction, an analogue of anethol would be formed.

† The production of anthracene derivatives could be accounted for in a similar manner :—



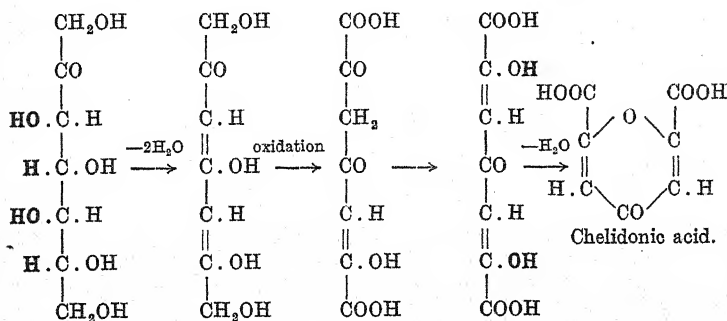
### 9. The Formation of Pyrones and Pyridines from Carbohydrates

The relations between the polyketides on the one hand and the pyrone and pyridine derivatives on the other have already been explained ; so two examples will be sufficient to indicate the possibility of a direct passage from the carbohydrate series to the two heterocyclic groups. As before, the atoms involved in the dehydrations are printed in heavy type.



10. *The Genesis of Some Plant Pigments*

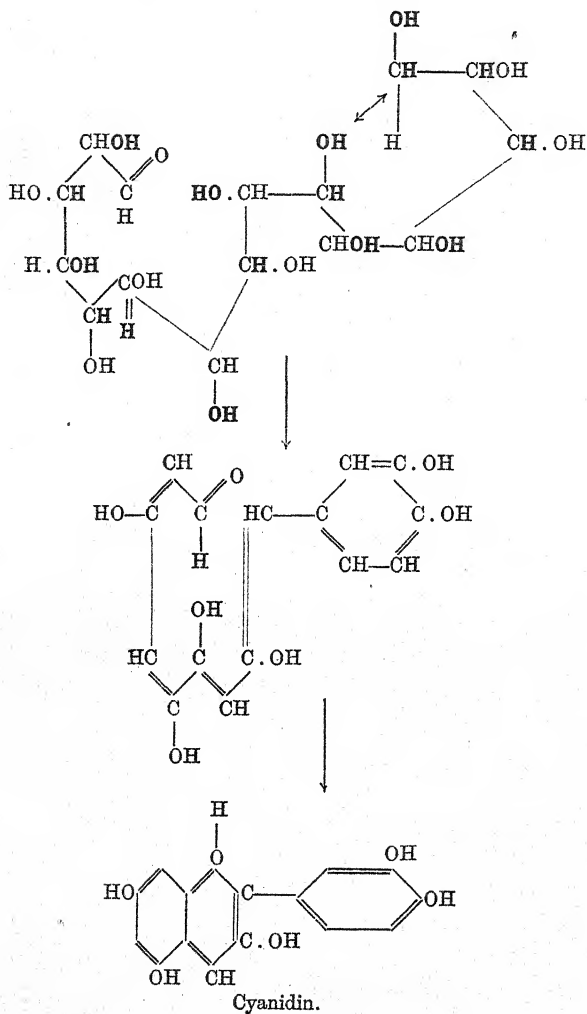
The fact that many of the important plant colouring materials belong to the pyrone group suggests that they may be derived from polyketide chains and hence, indirectly, from the celluloses. In the simpler colouring matters the connection is almost obvious from an inspection of the formulæ; and one example will suffice. Chelidonic acid may be chosen, and its possible derivation from a heptose accounted for by the usual processes of dehydration and oxidation:



The benzo-pyrone group can be accounted for in a similar manner.

In the case of the anthocyanins, the reaction may be traced directly back to a carbohydrate chain without requiring the intermediate formation of a polyketide derivative at all. An examination of the formula of cyanidin,  $\text{C}_{15}\text{H}_{12}\text{O}_6$ , shows that it might be derived from a carbohydrate having the composition  $\text{C}_{15}\text{H}_{30}\text{O}_{15}$  by the abstraction of nine molecules of water; and from cyanidin the corresponding anthocyanin is produced by the action of glucose. From the cyanidin, also, quercetin may be formed by oxidation; so that such a synthesis would open the way to the flavone series as well.

The following formulæ show how, by simple dehydration, it is possible to imagine the production of cyanidin from a carbohydrate of the structure  $\text{CH}_2\text{OH} \cdot (\text{CH} \cdot \text{OH})_{13} \cdot \text{CHO}$ . In order to make the steps clearer, the atoms eliminated by dehydration are printed in heavy type:



It is unnecessary to give further examples, as the reader can easily work them out for himself if he is interested in the point.

### 11. *The Alkaloidal Skeletons*

With regard to the formation of the alkaloids, two views are possible. In the first place, the alkaloidal skeleton may be supposed to come into existence directly by the action of

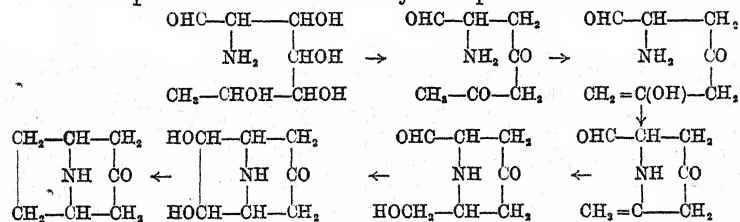


ammonia upon a long carbon chain derived from the celluloses; or, secondly, we may assume that the celluloses and proteins break down into smaller molecules which then take part in piecemeal syntheses of the larger alkaloid groupings. In either case, it will be seen that the production of alkaloids is to be regarded as a down-grade reaction.

The formation of tropinone furnishes a case to which both methods are applicable; so it may be given here as an example.

Let us assume that among the degradation products of cellulose a methyl-hexose-amine is produced. This will have the composition  $C_7H_{15}O_5N$ . Now *nor*-tropinone *i.e.* tropinone without the methyl radicle attached to the nitrogen atom has the composition  $C_7H_{11}ON$ . The difference between the two formulæ is  $H_4O_4$ ; from which it is clear that dehydration alone will not suffice to pass from the one compound to the other; reduction to the extent of four hydrogen atoms is also necessary.

The steps in the conversion may be represented as follows:—



All the dehydrations and rehydrations involved in the process have not been indicated in the formulæ, as by this time the reader is probably sufficiently expert in appreciating the method to dispense with some of the steps. The last stage shown above consists in a reduction of the dihydric alcohol to a hydrocarbon grouping, which accounts for the four extra hydrogen atoms already mentioned. Having thus reached *nor*-tropinone, methylation with formaldehyde would account for the production of tropinone itself.

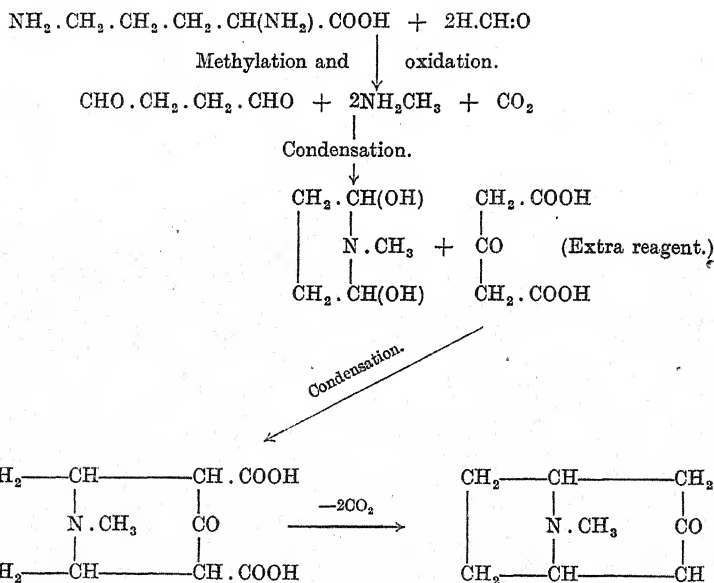
Of course the order in the above series of changes might be varied, some of them coming earlier than is shown. The methylation of the nitrogen atom, for example, might take place much sooner than has been assumed.

Robinson<sup>1</sup> has put forward a series of suggestions as to the manner in which many of the familiar alkaloidal skeletons may be produced by using comparatively simple reactions; and his

<sup>1</sup> Robinson, *J.*, 1917, 111, 876.

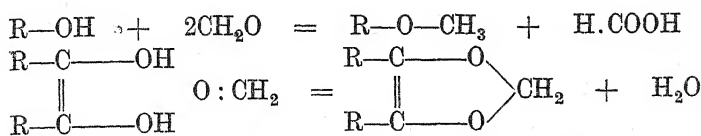
paper should be studied by all who are interested in the question. Unfortunately, it would lose by condensation, so cannot be dealt with here. In it examples are given of possible lines of syntheses in the pyrrolidine, piperidine, quinoline, and *isoquinoline* groups of alkaloids. Two reactions only are demanded as essential to the formation of the skeletons: the aldol condensation and the similar reaction between carbinolamines [containing the grouping  $R_2 : C(OH).N : R_2$ ] and compounds containing the radicle:  $CH.CO$ .

As an example of the method, we may choose the synthesis of tropinone—

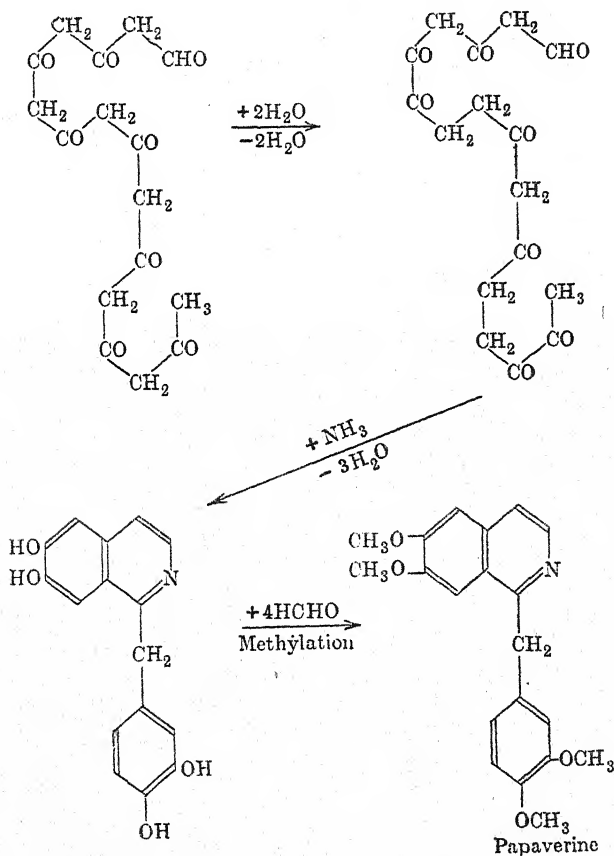


Robinson's synthesis of tropinone has shown that reactions of the type required by his views can actually take place in practice under ordinary conditions.

† Returning to the idea that the cellulose chain, *via* the polyketides, affords a source of alkaloid material, an example may be given of the course which the synthesis of papaverine might be expected to take. It must be pointed out that by the usual process of dehydration and rehydration, it is possible to pass from the grouping  $R.CO.CH_2.CO-$  to the arrangement  $R.CH_2.CO.CO-$ ; and also that the formation of methoxyl



radicles and methylene-ether groups may be supposed to take place by the action of formaldehyde. The steps in the papaverine synthesis are shown below.

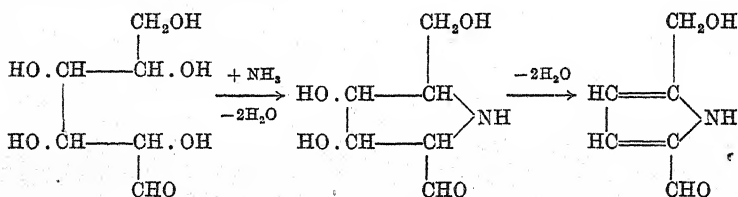


## 12. The Natural Syntheses of Pyrrol Derivatives

The importance of the pyrrol compounds from the standpoint of natural processes has already been indicated in an

earlier chapter. The assimilative machinery of plants is bound up with chlorophyll; whilst hæmin plays an analogous part in animals: and both these substances are built up on a basis of pyrrol rings. In addition to them, numerous other pyrrol derivatives are known to occur in the products of vegetable and animal metabolism: the pyrrolidine alkaloids and the bile acids are cases in point. It is therefore desirable to indicate here how these substances may be produced by vital reactions.

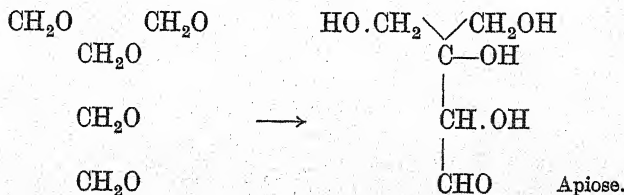
The carbohydrates probably form one source from which materials are drawn for pyrrol syntheses; whilst the nitrogen may be supplied either from ammonia or indirectly from the proteins. Assuming the presence of a sugar and ammonia, the synthesis of a pyrrol derivative may be accounted for by two dehydration reactions thus—



From a pentose, of course, a pyrrol with a single aldehydic side chain would be produced.

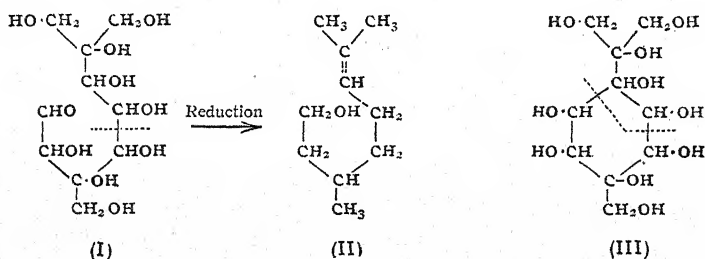
### 13. Branched Chains and Terpene Compounds

Hitherto we have confined our attention to carbohydrates in which the carbon atoms form a straight chain, but it seems desirable to indicate how forked chains may come into existence, as compounds of this type occur naturally along with straight-chain substances. The formation of apiose may be taken as an example. Its composition is  $\text{C}_5\text{H}_{10}\text{O}_5$ , and it might obviously be produced by the aldol condensation of five molecules of formaldehyde in the following manner:—



It seems difficult to imagine how apiose can be synthesized naturally in any other way.

But if this be granted, it becomes clear that terpene skeletons might be produced by an extension of the same series of condensations. Two possibilities are open. In the first place, two apiose nuclei may condense together giving the substance (I.) which by reduction may be transformed into an olefinic terpene derivative (II.); and from this, by intramolecular change similar to the geraniol-terpineol rearrangement, a terpene derivative might be formed. Or, alternatively, ten molecules of formaldehyde might condense together to produce a doubly-linked apiose chain (III.) from which terpenes might be formed by reduction.

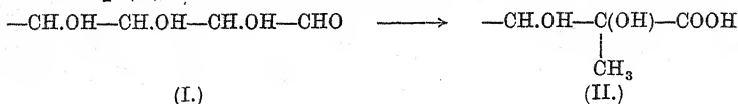


The particular terpene derivative formed would depend on the stage of oxidation of the original open-chain compound in the second case and also upon the position of the double bonds in the open chain.

Another possible line of synthesis of the terpenes is suggested by the production of a thymol derivative from the condensation products of orcinol and acetoacetic ester. Since the orcinol and the acetoacetic ester are both obtainable from polyketide chains, and hence possibly from carbohydrates; and since the thymol compound thus produced may be supposed to be reducible to a terpene, this line of thought leads also from the carbohydrates to the terpene group.

Finally it may be pointed out that a terpene  $\text{C}_{10}\text{H}_{16}$  could be derived from a carbohydrate  $\text{C}_{14}\text{H}_{28}\text{O}_{14}$  by the removal of four molecules of carbon dioxide and six molecules of water. In this case it would be necessary to assume as an intermediate compound one of those unsaturated acids which tend to lose their carboxyl radicles spontaneously.

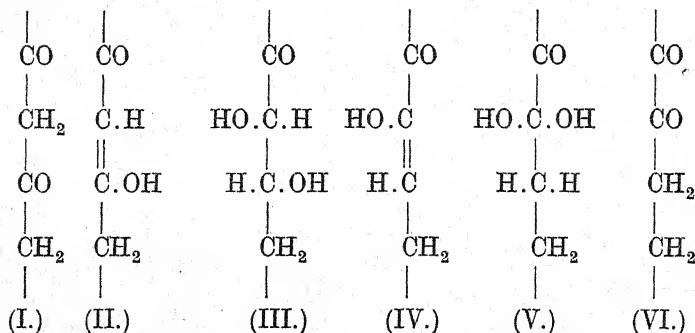
Other reactions which might lead to the formation of a forked chain are the condensation of formaldehyde with a straight sugar chain and subsequent dehydration of the aldol thus produced; or the peculiar rearrangements in the sugar group observed by Kiliani,<sup>1</sup> whereby, under the action of lime-water, the group (I.) is transformed into (II.):



or the analogous benzilic acid change.

#### 14. The Formation of Fats

For the production of fats in the animal body the carbohydrates absorbed as food form the most probable source. We have already seen that sugars may be converted into polyketide chains by dehydration, so it is not necessary to give these steps. We may commence with the polyketide chain shown in (I.) as an example:—



† If we take as our starting-point the group (I.) and convert it into the enolic form (II.), we can then add a molecule of water on to the double bond to form (III.). This substance could then be hydrated to produce (IV.), to which water might be again attached, giving (V.), in which two hydroxyl groups are attached to the same carbon atom. This compound would lose a molecule of water, leaving (VI.).

<sup>1</sup> Kiliani, *Ber.*, 1884, 17, 1302; 1905, 38, 2668; 1908, 41, 158, 469.



† A comparison of the formulæ (I.) and (VI.) shows that the whole process implies a wandering of the hydrogen atoms to the lower end of the chain, and a corresponding migration of the oxygen atoms to the other. This purely theoretical series of actions could then be repeated, and the final result would be a loss of carbon dioxide from one end of the chain, and a building up of an aliphatic chain at the other end. Some such process may take place in the living organism during the formation of oils or fats,\* and the liberation of carbon dioxide in respiration would be explicable in the same way.

Evidence in favour of this conception of the formation of fats from carbohydrates is obtained when the results of the reverse process are examined. In the disease pentosuria, the body fats are broken down and converted into sugars. Now, if this process involved the decomposition of the fat, with subsequent assimilation in the organism, then a synthesis of the pentose and, finally, its excretion, we should expect to find that the inactive fat had been converted into an *optically active* sugar owing to the intervention of the asymmetric components of the body tissues, etc. On the other hand, if the fat is converted direct into the sugar by the converse of the process sketched above—i.e., if the process involves a mere passage from Stage VI. to Stage I.—then, owing to the continual formation of enolic forms and consequent loss of asymmetry, the products of the fatty decomposition would not be active. In actual practice it is found that the arabinose excreted by patients suffering from pentosuria is the racemic form<sup>1</sup> of the compound; and this notwithstanding the fact that the organism is quite capable, even in that state, of decomposing *l*-arabinose if this sugar be given in food. It seems evident, therefore, that the arabinose excreted by such patients cannot have passed through the ordinary channels, but must have been produced directly from fat by some simple reaction such as is shown above. Further, the occurrence of acetoacetic acid and acetone along with sugar in the urine of patients suffering from diabetes proves that polyketide derivatives make their appearance during the disease.

\* Or wax in the case of bees.

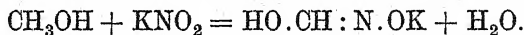
<sup>1</sup> Neuberg, *Ber.*, 1900, 33, 2243.



15. *Syntheses and Degradations of the Proteins*

In the foregoing sections we have dealt very fully with the carbohydrates and their possible mutations; so that it will be necessary to devote only a small space to the proteins, that second great class of up-grade products of the vital machinery. Fischer's researches on the polypeptides leave little doubt that the protein molecules contain long chains of amino-acids coupled together in the form of amides; and it remains to suggest methods whereby such substances could be synthesized from simple materials within the living organism.

As in the case of the carbohydrates, our knowledge of the initial steps in the process is incomplete. Nitrates appear to be assimilated by the plant and reduced to nitrites; but uncertainty exists as to the further fate of the nitrite when it has been formed. The most suggestive experiments on the subject appear to be those of Baudisch.<sup>1</sup> On exposing potassium nitrate to diffused daylight, he found that it was reduced to potassium nitrite. Under the same conditions, potassium nitrite, when mixed with formaldehyde or methyl alcohol, became converted into hyponitrite and then, by the action of more methyl alcohol, was changed into the potassium salt of formohydroxamic acid:



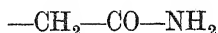
Prolonged exposure to light resulted in a further reduction, ammonia being formed.

According to Baudisch, ammonia in plants is oxidized by oxidases or by ultra-violet light, and the resulting product combines with formaldehyde to form aci-nitromethane which, being a reactive substance, takes part in vegetable syntheses.

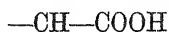
If we assume the presence of ammonia and carbohydrates, however, the further reactions may be formulated in other ways. Since unripe plants contain a high percentage of amides, we may postulate that the first step in the synthesis of the proteins is the production of an amide. We are then faced with a certain difficulty; for it is clear that an inversion of some kind must take place in order to convert the group (I.) into the group (II.),

<sup>1</sup> Baudisch, *Ber.*, 1911, 44, 1009.

which entails the transference of the nitrogen atom from one carbon atom to the next

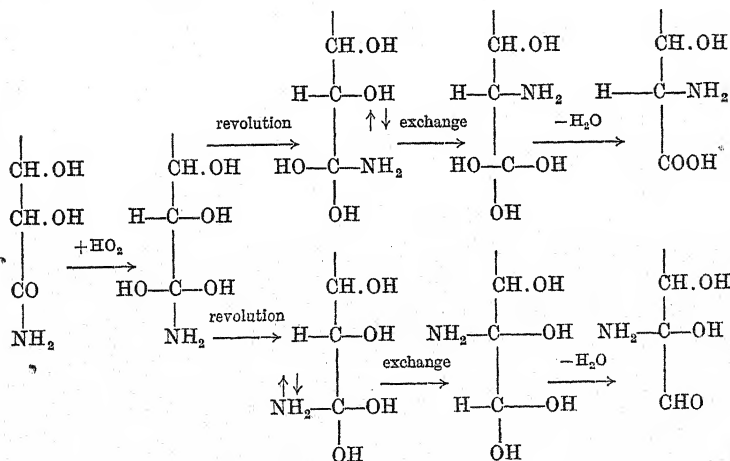


(I.)

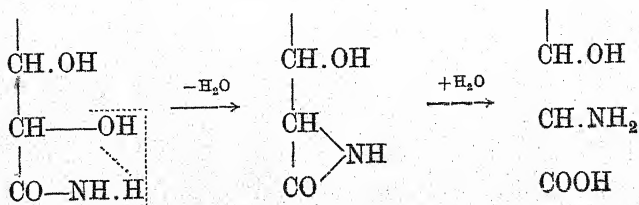


(II.)

† Such transferences are quite possible on lines with which we are already familiar. The following symbols show the application of the pinacol rearrangement to the problem:—

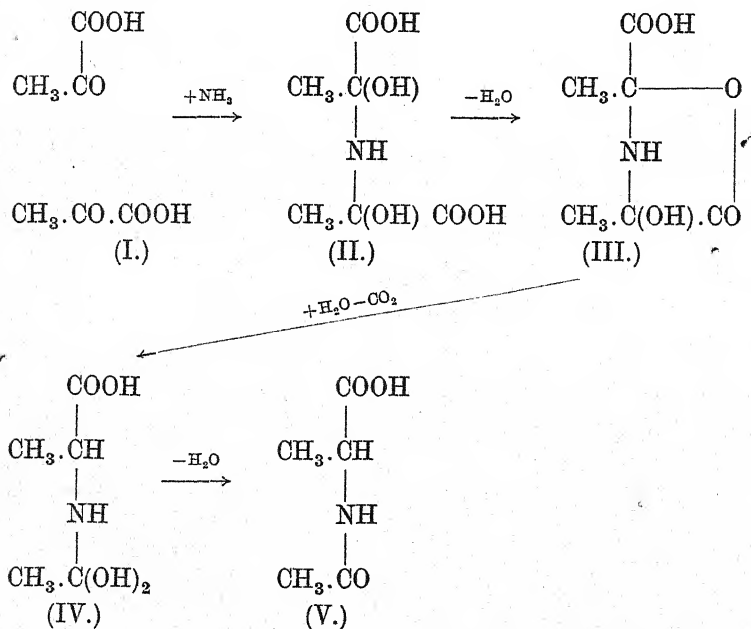


Another method by which the transference of the nitrogen atom to the neighbouring carbon might be accomplished is by the temporary production of a three-membered ring which, as soon as formed, might open up again in a new place. In this way the reaction is reduced to the simple subtraction and readdition of a molecule of water—



The production of the original amide radicle may be attributed to the formation and partial hydrolysis of a cyanhydrin of the sugar; for hydrocyanic acid is known to be formed in plants in quantities sufficient to yield the required cyanhydrins.

Much more probable than either of the above suggestions is the following, which is based upon an observation of de Jong<sup>1</sup> in the case of pyruvic acid. When ammonium pyruvate is mixed with pyruvic acid the reaction takes the following course. In the first place the two pyruvic molecules (I.) react with ammonia from the ammonium salt to form an imino-compound (II.). This substance then loses water, and forms the lactone (III.). A molecule of water is then taken up and carbon dioxide is split off, yielding the substance (IV.), which immediately eliminates another molecule of water, producing  $\alpha$ -acetyl-amino-propionic acid (V.):

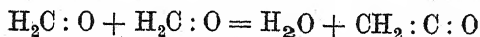


Now it will be seen that this reaction leads to the formation of the type of amino-acid most common among the protein derivatives—the  $\alpha$ -amino-acid; for the acetyl group could easily be hydrolysed away by enzyme action.

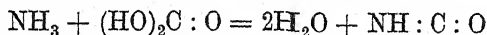
<sup>1</sup> De Jong, *Rec. trav. chim.*, 1900, 19, 259; 1904, 23, 131.

The application of this to more complex cases is not difficult. It will be remembered that in the section dealing with the formation of fats it was pointed out that a very simple process would lead from the carbohydrates of the type  $R-CH.OH-CH.OH-CH.OH-CH.OH-CHO$  to derivatives of the structure  $R-CH_2-CH_2-CO-CO-COOH$ . Oxidation of the latter would yield homologues of pyruvic acid, the number of carbon atoms in the group R depending upon the length of the carbohydrate chain which serves as a raw material. Once these pyruvic acid derivatives have been produced, there is no reason why they should not undergo de Jong's reaction and form the corresponding  $\alpha$ -amino-acids; and in this way the raw materials for polypeptide and protein syntheses might be produced.<sup>1</sup>

In connection with the protein syntheses, another point of interest arises, though it must be classed as a purely speculative one. If two molecules of formaldehyde could be induced to condense together in the following manner, keten would be formed; and from this, by polymerization, chains of polyketide might be formed:



Now, similarly, we might devise a synthesis in the nitrogen group:

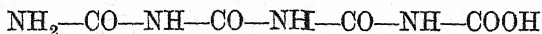


This compound is, of course, isomeric with cyanic acid.

† For present purposes, however, our interest in it arises from the fact that it is obviously the nitrogen analogue of keten:



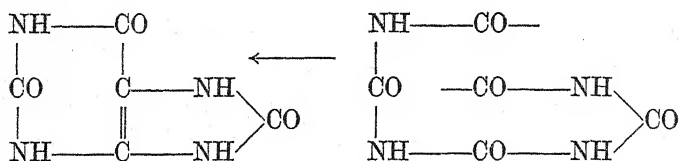
and, from this similarity, we may term the compound aziketen. Now just as keten can polymerize to long chains which then add on water to form polyketides, so aziketen should polymerize and hydrate in order to produce the simplest type of polypeptide—



† It is at this point desirable to bring the matter into touch with actual practice. If we examine the formula of uric acid, it requires no great stretch of imagination to recognize that

<sup>1</sup> For other suggestions see Haas and Hill, *Chemistry of Plant Products* (1917), pp. 333 ff.

the purine compounds are derivatives of this type of polypeptide, probably produced from the open-chain compound by reduction accompanied by ring formation :



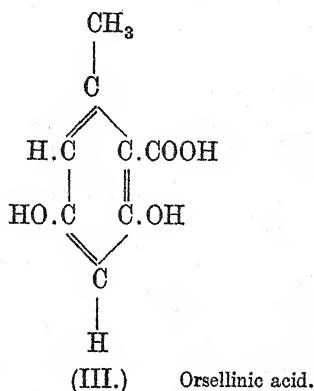
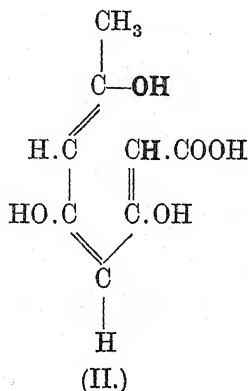
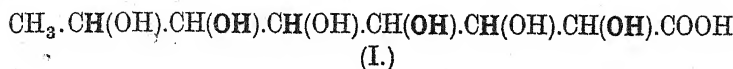
Thus the break-down of the sugars into the various aromatic and pyrone derivatives would find its analogue in the formation of the uric acid derivatives from the proteins.

† Another suggestion as to the production of purine derivatives by vital processes may be put forward. In the break-down of proteins, amino-acids of the type  $\text{R}-\text{CH}(\text{NH}_2)-\text{COOH}$  are formed. Now in the oxidation of these, it is possible that the hydrocarbon chain R is burned away first, leaving behind the potential  $-\text{NH}.\text{CO}-$  portions, which may then unite to form uric acid and its derivatives.

### 16. *The Carbohydrates and the Depsides*

The application of Collie's views to the formation of natural depsides can be illustrated by the case of the moss acids. Here the fundamental skeleton is to be found in orsellinic acid ; and the starting-point would be an acid derived from a methylheptose (I.). Removal of three molecules of water, as indicated by the heavy type of this formula, would produce the polyketide derivative (II.), which is obviously an enolic derivative of the straight-chain tetracetic acid. A further loss of one molecule of water by elimination of the atoms shown in heavy type would yield orsellinic acid (III.).

The production of orsellinic acid would lead on to the syntheses of the remaining moss acids. By esterifying the carboxyl group of one molecule of orsellinic acid with a hydroxyl group belonging to another molecule, lecanoric acid would be formed. The methylation of one hydroxyl group of orsellinic acid would yield everninic acid ; and a combination of the remaining hydroxyl radicle of this with a second molecule of orsellinic acid would produce evernic acid.



It is thus evident that Collie's ideas are capable of accounting for the changes necessary to convert a carbohydrate into the principal moss depside derivatives.

### 17. Conclusion

In this chapter an attempt has been made to sketch certain methods by which natural products may possibly come into existence in the organism, but it cannot be too strongly emphasized that they are intended merely as suggestions and not as dogmatic attempts to settle the problems involved. If they have brought to the notice of the reader the questions which arise in this branch of chemistry and have inspired any desire to go further into the matter, they have amply fulfilled the object for which they were written. We are at present far from a definite knowledge of how the vital machine carries out its work; but if the ideas collected in the present chapter induce the reader to speculate for himself on the subject, he will find a most fascinating field open to him.


One point which certainly comes into prominence in the foregoing pages is the fact that, by a series of hypothetical dehydrations and rehydrations, it is easy to see how very different types of grouping might be produced. A system which is capable of accounting for the production of such widely varying materials as benzene derivatives, pyrroles, pyridine derivatives,



pyrones, anthocyanins, depsides, fats and alkaloids has evidently something more than mere plausibility behind it. We are not yet able to carry out these changes in the laboratory, except in the case of the polyketide derivatives; but it will be surprising if sooner or later some experimental evidence is not found to bear out much that has been advanced in the preceding sections.

† Should the reader wish to pursue speculations in this field the following questions may serve to guide his attention to some hitherto unsolved problems. The fatty acids of the acetic series are quite common in nature, whilst their hydroxy-derivatives—with the exception of lactic acid—are hardly represented at all. Why should this be so? Why do all the important sugars and starches contain a chain of five or six or a multiple of five or six carbon atoms? Why are the majority of the amino-acids obtained from the proteins the  $\alpha$ -amino-acids? Why are the *ortho*- and *meta*-derivatives so strongly represented among naturally occurring benzene derivatives, whilst the majority of the terpenes are derived from *para*-cymene?

† In such broad generalities there must surely be some simple solution. The curious thing is—not that the answers to these questions are omitted from the ordinary text-books, but rather that the questions do not appear to have suggested themselves to the writers at all.





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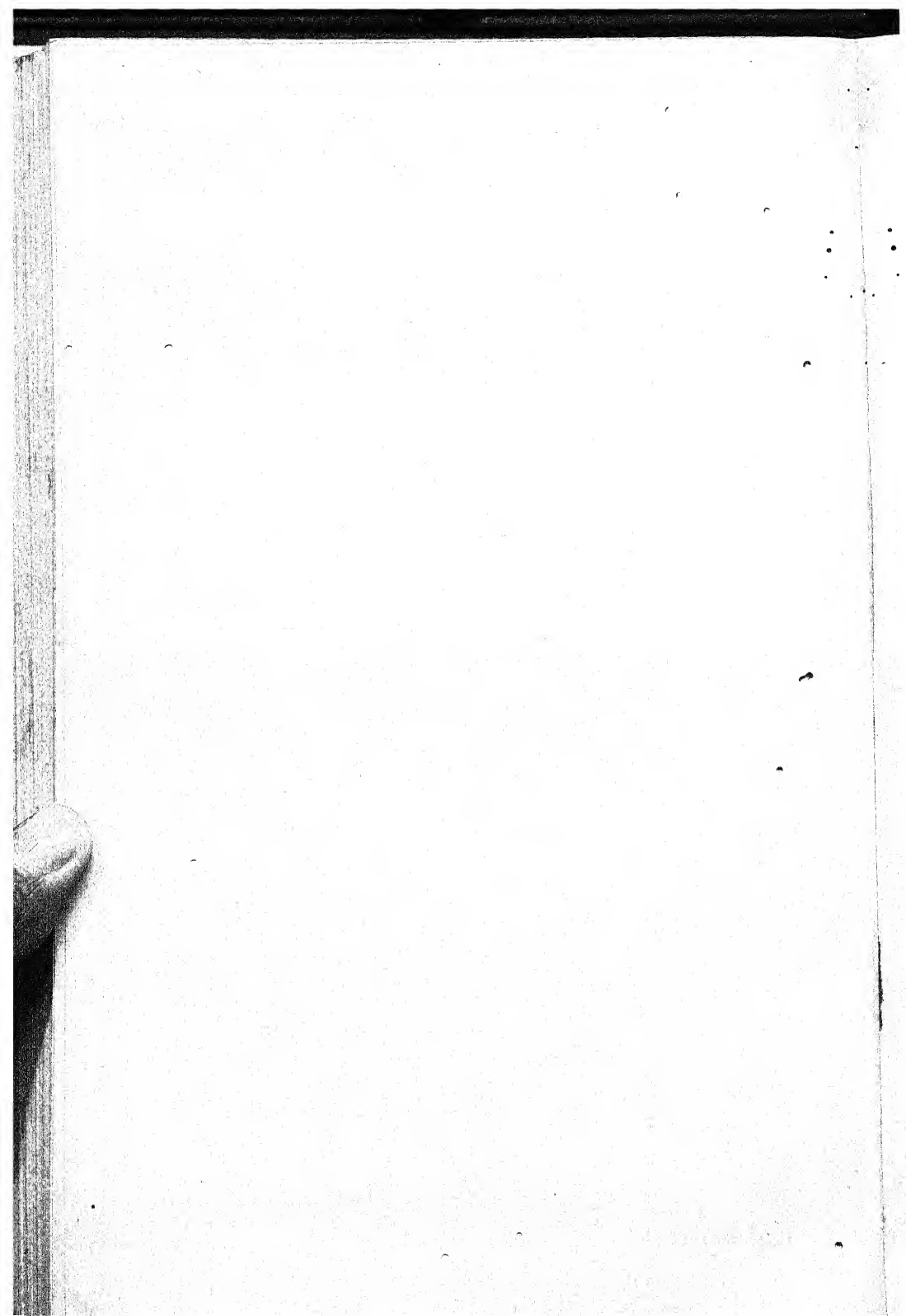
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